Draft Comparative Effectiveness Review

Number XX

Pressure Ulcer Treatment Strategies: A Comparative Effectiveness Review

Prepared for:
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AHRQ Publication No. XX-EHCXXx
<Month Year>

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: <Authors>. <Topic>. Evidence Report/Technology Assessment. No. <#>. (Prepared by <EPC Name> under Contract No. <##>.) Rockville, MD: Agency for Healthcare Research and Quality. <Month, Year>. http://www.ahrq.gov/clinic/epcix.htm. Accessed: <Date>. <URL>.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: <Acknowledgments>.

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Pressure Ulcer Treatment Strategies: A Comparative Effectiveness Review

Structured Abstract

Objectives: With up to 3 million Americans suffering from pressure ulcers, pressure ulcers are a major source of morbidity, mortality, and cost for US health care. The objective of this review is to summarize the available evidence comparing the effectiveness and safety of treatment strategies for pressure ulcers.

Data Sources: Articles were identified from searches (conducted between January 1, 1985 to August 5, 2011) of MEDLINE (Ovid), Embase (Elsevier), CINAHL (EBSCOhost), EBM Reviews (Ovid), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment. Additional studies were identified through hand searching of reference lists from included studies and from systematic reviews of pressure ulcer treatments. Grey literature including unpublished data, abstracts, dissertations, and individual product packets from manufacturers were also searched or solicited.

Review Methods: Two reviewers independently reviewed the literature using predefined criteria to select randomized trials and observational studies. Results were summarized in evidence tables and the quality of included studies and extracted data were dually reviewed to ensure accuracy. Summary results were derived primarily from qualitative analysis and synthesis of data across individual studies. Meta-analysis was limited to only select treatment comparisons due to the small number, poor quality, and heterogeneity of studies for most treatment comparisons.

Results: From the 6,463 titles and abstracts, we reviewed 1,382 full-length articles and included 165 studies addressing the effectiveness and/or harms of different modalities for treating pressure ulcers. *Support surfaces:* We found moderate-strength evidence for the following: air-fluidized beds are superior to other support surfaces, different mattress brands are comparable in performance, and there is no overall benefit to low air-loss beds compared to standard foam mattresses. Evidence on the effectiveness of alternating pressure surfaces was inconclusive. The harms of different support surface options were minimal. *Nutritional supplementation:* Studies of mixed nutritional supplementation and studies of protein or amino acid supplementation provided low strength of evidence to suggest a possible small wound healing benefit for these two types of interventions. *Local wound applications:* We reviewed comparisons of a wide variety of modern wound dressings and found low-strength evidence that hydrocolloid dressings are superior to gauze and moderate-strength evidence that hydrocolloid and foam (hydrocellular or polyurethane) dressings produced similar wound healing results. Evidence about the comparative effectiveness of other types of dressings was insufficient to draw conclusions. We found moderate-strength evidence that radiant heat dressings accelerated the rate healing compared to other dressings, although there was no evidence of benefit in terms of complete wound healing. Among the evaluated topical therapies we found insufficient evidence on the effectiveness of debriding enzymes (e.g., collagenase). There was low-strength evidence that wound healing was similar with collagen compared to standard care, and that dextranomer was

less effective than standard wound dressings or other topical agents. Evidence about phenytoin was insufficient to draw conclusions. Studies of biological agents provided low-strength evidence that platelet-derived growth factor demonstrates some benefit compared to placebo in promoting healing of severe (stage III or IV) ulcers. There was insufficient evidence about the effectiveness of other types of biological agents. Evidence was also insufficient to make conclusions about the effectiveness or harms of local wound applications across different ulcer or patient characteristics, or settings. *Surgical interventions:* All findings related to the comparative effectiveness and harms of surgical interventions were based on low-strength evidence. These findings included a lower rate of ulcer recurrence with sacral ulcers compared with ischial ulcers, a higher rate of recurrent ulcers among patients with spinal cord injury compared with others; greater wound dehiscence rates with myocutaneous compared to fasciocutaneous flaps and with surgeries in which bone is removed as part of the operation; and more adverse events with surgery for ischial compared to sacral or trochanteric ulcers. Surgical flap failures requiring reoperation ranged from 12 to 24 percent. *Adjunctive therapies:* We found moderate-strength evidence that electrical stimulation improved healing rates, but inconclusive evidence about the effect of electrical stimulation on complete wound healing due to heterogeneous findings across studies. Low-strength evidence indicated that the most common adverse effect of electrical stimulation was local skin irritation, and that harms were more common in frail elderly compared to younger populations. There was also low-strength evidence for the following: electromagnetic therapy, therapeutic ultrasound, and negative pressure wound therapy produced wound healing results similar to sham treatment or standard care; light therapy provided a benefit in terms of wound area reduction but not complete wound healing, and was not associated with significant adverse events compared to sham or standard care; and laser therapy was not associated with significant adverse events, but produced wound healing results similar to sham or standard treatment. There was insufficient evidence to evaluate the harms of those adjunctive therapies.

Limitations: Limitations of the evidence base in our review were related to poor study quality, studies with inadequate followup periods to assess complete wound healing, and the heterogeneity of methods for measuring wound healing outcomes.

Conclusions: We found limited evidence to draw firm conclusions about the best approaches for treating pressure ulcers, a finding that is consistent with other recent reviews on this topic. Future research with larger sample sizes, more rigorous adherence to methodological standards for clinical trials, longer followup periods, and more standardized and clinically meaningful outcome measures is needed to inform clinical practice and policy.

Contents

Tables

Figures

Appendixes

Pressure Ulcer Treatment Strategies: A Comparative Effectiveness Review

Executive Summary

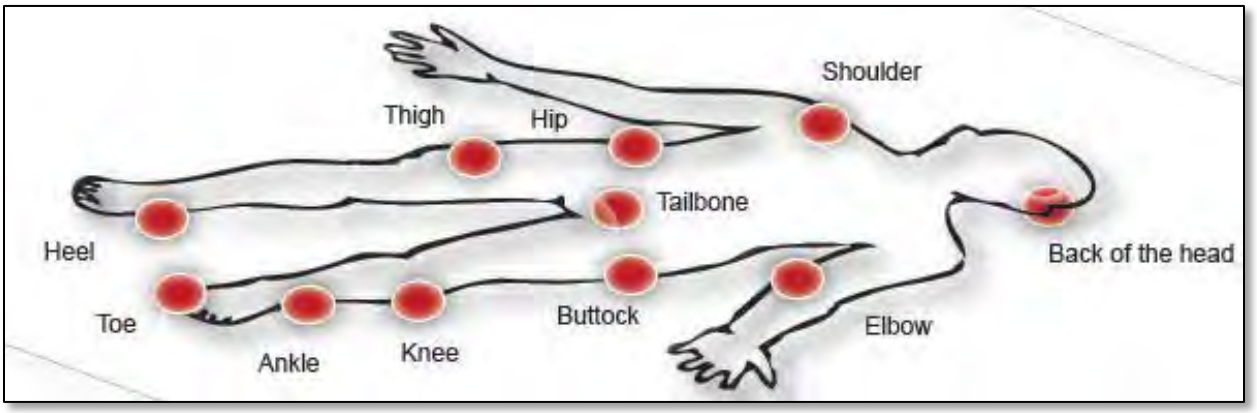
The Effective Health Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov. Ahrq.gov/reports/final.cfm

Background

Uninterrupted pressure exerted on the skin, soft tissue, muscle, and bone can lead to the development of localized ischemia, tissue inflammation, tissue anoxia, and necrosis. Pressure ulcers affect three million adults in the United States. Common areas of the body prone to the development of pressure ulcers are depicted in Figure A. Estimates of the incidence of pressure ulcers vary according to the setting, with ranges of 0.4 to 38.0 percent in acute-care hospitals, 2.2 to 23.9 percent in long-term nursing facilities, and 0 to 17 percent in home care.[1, 2]

Figure A. Common pressure ulcer sites



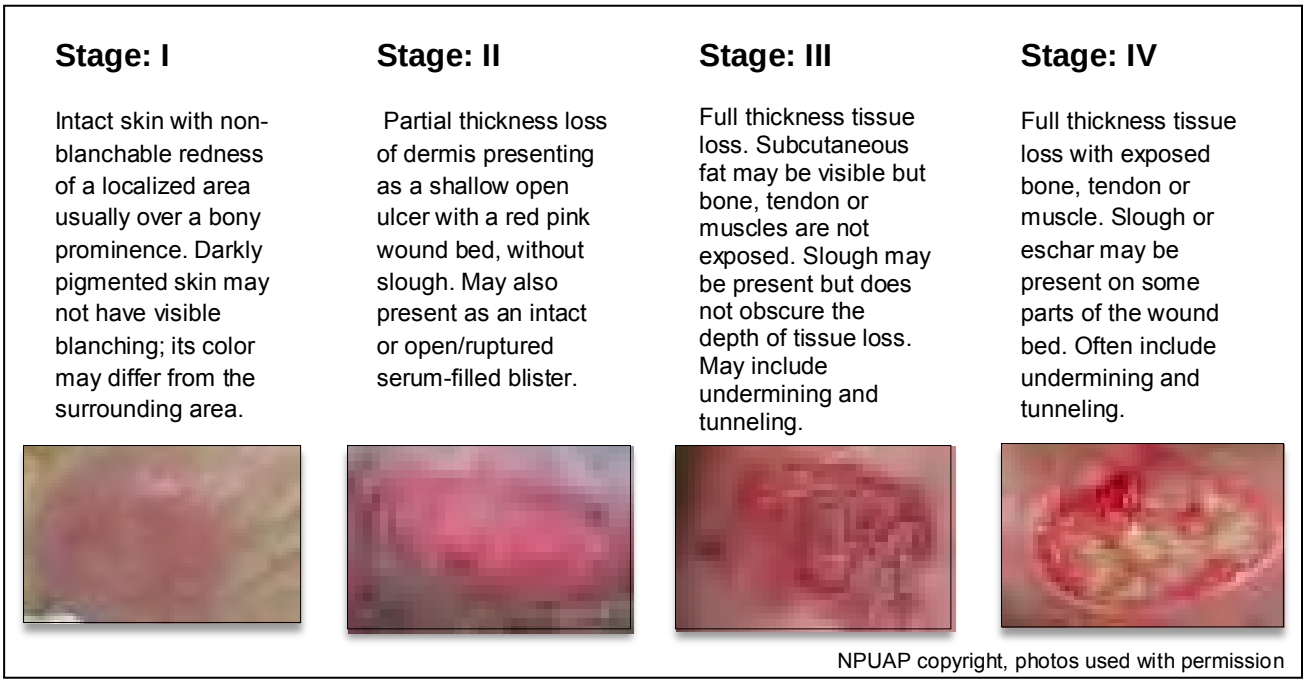
EPC

Pressure ulcer healing rates, which are dependent on comorbidities, clinical interventions, and severity of the ulcer, vary considerably. Ulcer severity is assessed using a variety of different staging or grading systems; the National Pressure Ulcer Advisory Panel (NPUAP) staging system is the most commonly used (Figure B). Comorbidities predisposing to pressure ulcer development and affecting ulcer healing include those affecting patient mobility (e.g., spinal cord injury), wound environments (e.g., incontinence), and wound healing (e.g., diabetes,

vascular disease). Delayed healing can add to the length of hospitalization and impede return to full functioning.[2] Data on the costs of treatment for a pressure ulcer vary, but some estimates range between $37,800 and $70,000, with total annual costs in the United States as high as $11 billion.[1, 3]

Given the negative impact PUs have on health status and patient quality of life, as well as health care costs, treatments are needed that promote healing, shorten healing time, minimize the risk of complications, and increase the likelihood of complete healing. Pressure ulcer treatment involves a variety of different approaches, including interventions to treat the conditions that give rise to pressure ulcers (support surfaces, nutritional support), interventions to protect and promote healing of the ulcer itself (wound dressings, topical applications, and various adjunctive therapies including vacuum-assisted closure, ultrasound therapy, electrical stimulation, and hyperbaric oxygen therapy), and surgical repair of the ulcer.[1, 3] Most ulcers are treated using a combination of these approaches. Standards of care for pressure ulcer treatment are typically guided by clinical practice guidelines, such as those developed by the NPUAP, but also vary by patient-related factors such as comorbidities and nutritional status,[4] local practice patterns, and the stage and features of the wound. Current guidelines primarily reflect expert opinions. An examination of the comparative effectiveness and harms of the wide variety of different therapies and approaches to treating pressure ulcers is important to guide clinical practice.

Figure B. National Pressure Ulcer Advisory Panel pressure ulcer stages



Scope and Key Questions

The following key questions are the focus of our report:

Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?

Key Question 1a. Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?

Key Question 1b. Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including but not limited to: age; race/ethnicity; body weight; specific medical comorbidities; and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?

Key Question 1c. Does the comparative effectiveness of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

Key Question 2. What are the harms of treatments for pressure ulcers?

Key Question 2a. Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?

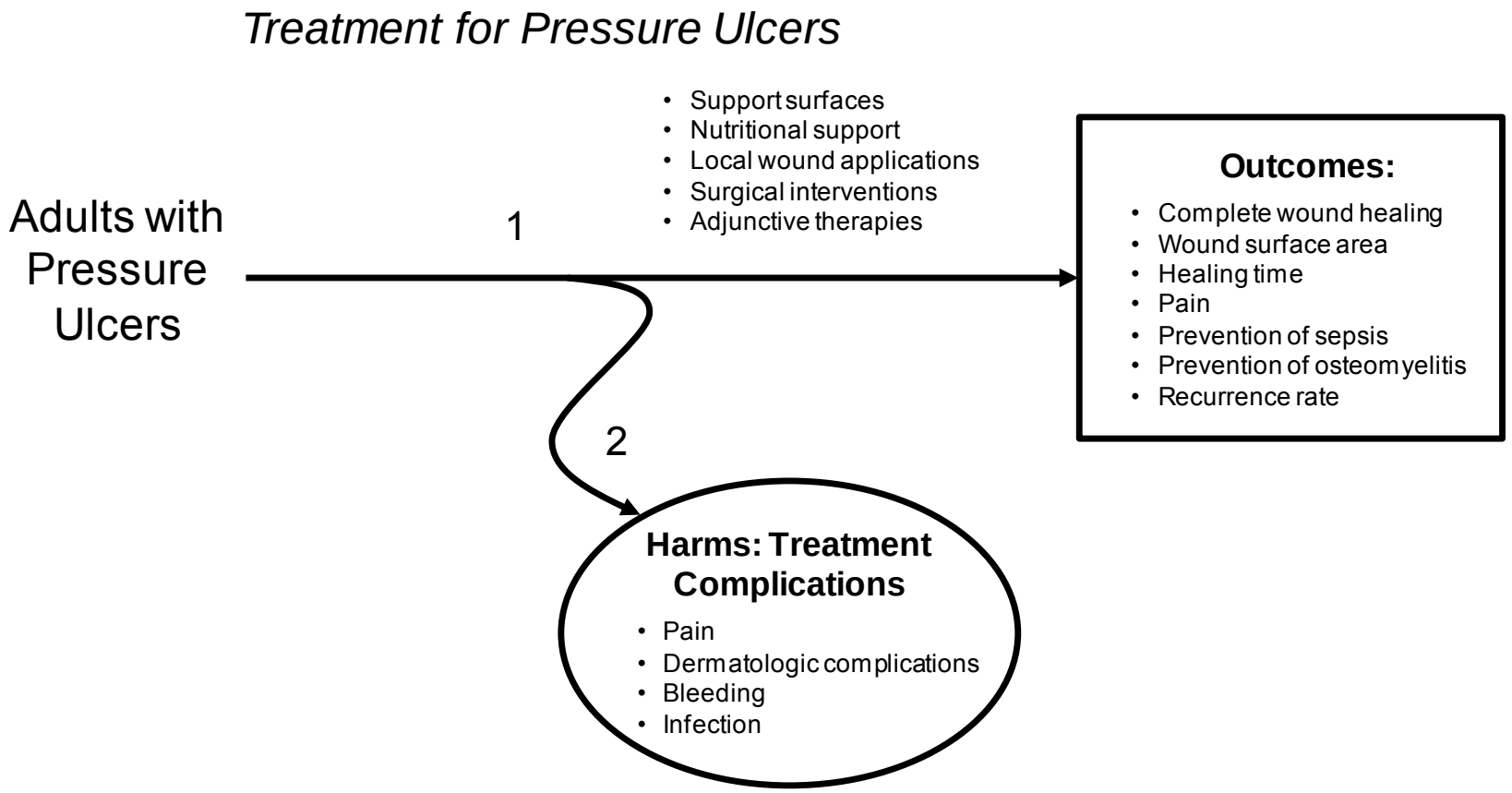
Key Question 2b. Do the harms of treatment strategies differ according to patient characteristics, including: age, race/ethnicity; body weight; specific medical comorbidities; and knows risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?

Key Question 2c. Do the harms of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

Analytic Framework

The analytic framework (Figure C) depicts the key questions in the framework of the population, interventions, outcomes, and harms considered in the review.

Figure C. Analytic framework: Pressure ulcer treatment strategies



Population and Conditions of Interest

The population studied was adults ages 18 and older with a pressure ulcer. Patients with pressure ulcers usually also have limited or impaired mobility and suffer from other chronic illnesses. Pressure ulcers are most common in the elderly or people with spinal cord injuries or other conditions that restrict movement and mobility. Patients with non pressure-related ulcers, including but not limited to venous ulcers and diabetic foot ulcers, were excluded because treatment considerations for these patients may differ significantly from those for pressure ulcers. We excluded children because this topic was originally nominated and scoped for adults.[a] Key informants agreed with the broadly defined proposed population of interest as "adults with pressure ulcers." They endorsed the proposed list of included patient characteristics that should be considered, but they also noted that "adults with pressure ulcers" is a heterogeneous group and that variability in the comparative effectiveness of pressure ulcer treatments may be related to a large number of patient characteristics. In addition to sex, race/ethnicity, socioeconomic status, and diverse specific medical comorbidities (e.g., diabetes, end-stage renal disease, dementia), many informants suggested that we include specific known risk factors for pressure ulcers (e.g., nutritional status, incontinence, peripheral vascular disease, mobility limitations, functional ability).

Interventions and Comparators

Various treatment strategies for pressure ulcers were addressed, including but not limited to therapies that address the underlying contributing factors (e.g., support surfaces and nutritional supplements), therapies that address local wound care (e.g., wound dressings, topical therapies, and biological agents), surgical repair, and adjunctive therapies (e.g., physical therapy).

Combined treatment modalities (cointerventions) were also evaluated (such as comparison of two treatments in combination, compared with a single treatment).

Comparators included placebo or active control, usual care, or other interventions.

Outcomes

The most commonly examined outcomes were various measures of wound healing. Some studies examined complete wound healing as the primary outcome, though many studies evaluated wound size reduction. Based on input from our TEP, we considered complete wound healing to be the principal health outcome of interest. However, we also considered wound size reduction to be an important outcome, because: a) it represents a necessary intermediate step towards the principal outcome of complete wound healing (i.e., complete wound healing can be considered 100% wound size reduction); b) the likelihood of complete wound healing is lower for larger or higher-stage ulcers, and therapies deployed for more advanced ulcers may not be expected to achieve complete wound healing over the course of several weeks, which was the duration of most of the studies in our review. Thus, in summarizing the evidence about a given treatment, we considered both complete wound healing and wound size reduction as part of the

[a] Although treatment approaches for children with pressure ulcers may be similar, other factors may influence the effectiveness differently in this population, including setting, caregiver attention, healing potential and comorbidities.

overall outcome of "wound healing," but we gave more weight to evidence of complete wound healing. Other outcomes included wound healing rate and time, pain, and avoidance of serious complications of infection.

For harms of treatment we evaluated pain, dermatologic complications, bleeding, infection, and other adverse outcomes as reported in identified studies.

Timing

We did not apply minimum followup duration for studies.

Setting

Settings included patient care settings, such as home, nursing facility, or hospital.

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[5] and the standards suggested by the Institute of Medicine for conducting systematic reviews.[6]

Topic Refinement and Review Protocol

The key questions for this CER were developed with input from key informants, representing clinicians, wound care researchers, and patient advocates, who helped refine key questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised key questions were then posted to the AHRQ public Web site for a four-week comment period, which concluded June 9, 2011. The Agency for Healthcare Research and Quality and the EPC agreed upon the final key questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report. We then drafted a protocol for the CER, which was reviewed by the TEP and is available from the AHRQ Web site (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=838&pageaction=displayproduct).

A multidisciplinary group of clinicians, researchers, and patient advocates with expertise in pressure ulcer treatment and research was selected to serve as TEP members to provide high-level content and methodological expertise throughout the development of the review. Participants included leaders in the areas of pressure ulcer treatment and research, wound care and physical therapy, and plastic and reconstructive surgery, as well as patient safety advocacy and national pressure ulcer treatment advisory panel members.

TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the authors reviewed the disclosures and determined the panel members had no conflicts of interest that precluded participation.

Search Strategy

For the primary literature we searched MEDLINE (Ovid), Embase (Elsevier), CINAHL (EBSCOhost), EBM Reviews (Ovid), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment. We searched broadly for pressure ulcer treatments with a date range of

1985-2011. Grey literature was identified by soliciting stakeholders, TEP recommendations, and searching relevant Web sites, including clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, and the WHO International Clinical Trials Registry Platform), regulatory documents (Drugs@FDA and Devices@FDA), conference proceedings and dissertations (Conference Papers Index [ProQuest CSA]), Scopus (Elsevier), Dissertations & Theses (ProQuest UMI), and individual product Web sites. An additional focused search strategy on hyperbaric oxygen for the treatment of pressure ulcers was conducted at the recommendation of our TEP due to the paucity of evidence on this subject obtained from the original search. We conducted a second search in MEDLINE (Ovid) for references of hyperbaric oxygen in conjunction with pressure ulcer treatment.

Scientific information packets (SIPs) were requested from identified drug and device manufacturers, and a notice inviting submission of relevant scientific information was published in the Federal Register. All interested parties had the opportunity to submit data for this review using the AHRQ Effective Health Care publicly accessible online SIP portal (http://effectivehealthcare.ahrq.gov/index.cfm/submit-scientific-information-packets/). Reviewers evaluated received SIPs for data relevant to our review.

Additional studies were identified by reviewing the reference lists of published clinical trials, systematic reviews, and review articles.

The literature searches will be updated during the peer review process, at which time the additional studies will be evaluated and those meeting the inclusion criteria will be synthesized for the review.

Inclusion and Exclusion Criteria

The criteria for inclusion and exclusion of studies were based on the key questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. We used the following inclusion and exclusion criteria (See Appendix B for details):

The criteria for inclusion and exclusion of studies were based on the key questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. We used the following inclusion criteria (See Appendix B for details):

Populations: Studies were limited to adults aged 18 years and older being treated for existing decubitus ulcers. Subgroups included sex, race/ethnicity, socioeconomic status, and diverse specific medical comorbidities (e.g., diabetes, end-stage renal disease, dementia), and patients with specific known risk factors for pressure ulcers (e.g., nutritional status, incontinence, peripheral vascular disease, mobility limitations, functional ability). Studies conducted in populations including children, adolescents, and patients with non pressure-related ulcers, including but not limited to venous ulcers and diabetic foot ulcers, were excluded because treatment considerations for these patients may differ significantly from those for pressure ulcers.

Interventions: For efficacy and effectiveness assessments, all studies of interventions for treatment of pressure ulcers meeting the requirements of the PICOTS and Key Questions were included. Treatments for pressure ulcers included, but were not limited to: support surfaces, nutritional supplementation, wound debridement and cleansing, wound dressings, biologic agents, and surgical repair. Adjunctive therapies included ultrasound, electrical stimulation, vacuum-assisted closure, and hyperbaric oxygen therapy.

Comparators: Included usual care, placebo, no treatment, or different treatment interventions. Studies with no comparator were included for the assessment of harms only.

Outcomes: Studies reporting clinical outcomes of complete wound healing, wound surface area reduction, pain, prevention of sepsis, prevention of osteomyelitis, recurrence rate and harms of treatment care settings, (including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training) were included. Studies of non-healing ulcers were not included. We excluded studies that only evaluated non-clinical outcomes, cost, comfort, or nursing time required to administer the intervention.

Timing: No minimum followup time was required. Studies published prior to 1985 were not included.

Setting: We included studies conducted in patient-care settings such as home, nursing facility, or hospitals. We excluded studies in hospice settings if complete wound healing was not an outcome measured.

Study design: We included randomized trials, cohort studies, and case-control studies pertinent to all key questions. If such studies were not available, we included cross-sectional studies and intervention series studies. We included multicenter surgical intervention series with a population of 100 patients or more. Systematic reviews were used as background information or to ensure completeness of the literature search. Case studies of only one patient were not included.

An initial scan of the literature revealed that studies of surgical interventions included primarily small series of specific surgical techniques performed at single centers. Because surgical outcomes are heavily influenced by individual surgeons, local practice patterns, and other contextual factors, our TEP raised concern that data from these small single-site studies ($n< 50$) would have limited generalizability, and that they would not provide a sound basis for making indirect comparisons across studies. We therefore excluded small single-site studies reporting the results of specific surgical techniques for pressure ulcer management. We originally planned to include only multicenter studies, but due to a paucity of evidence, based on input from our TEP, we expanded our inclusion criteria to include single-center studies reporting a large series($n\geq 50$) of patients undergoing surgery for pressure ulcer, as these were felt to have greater generalizability. We included studies that provide direct, head-to-head comparisons of different surgical techniques.

According to guidance from the European Pressure Ulcer Advisory Panel (EPUAP), and suggestions of literature from our Key Informants, the most relevant evidence about modalities and procedures for treating pressure ulcers used in clinical practice today comes from investigations conducted within the past 25 years therefore we limited the search to 1985 to present. Guidance from our TEP indicated that current literature (1985 to present) not only captures historically significant treatments and evidence, but also provides the most current information and treatments currently used in clinical practice. Non-English language studies were included in the abstract triage and translated for full-text review as feasible. Grey literature including unpublished data, abstracts, dissertations, and individual product packets from manufacturers were solicited, to be included if they added meaningful data or other information beyond what is found in the published literature.

Study Selection

To enhance consistency and reduce bias in our study selection process each reviewer evaluated the same set of 200 citations for inclusion and kappa values were calculated to estimate inter-reviewer reliability. After discussing and reconciling disagreements between reviewers, the same four team members reviewed an additional 100 citations. This process was continued until a kappa value of >0.50 for each pair of reviewers was reached. For the remaining references each reviewer evaluated each title and abstract for inclusion and exclusion, using the pre-established inclusion/exclusion criteria to determine eligibility for inclusion in the evidence synthesis. To ensure accuracy, a senior investigator/clinician conducted secondary reviews of all excluded abstracts. All citations deemed appropriate for inclusion by one or both of the reviewers were retrieved for full-text review.

Each full-text article was independently reviewed by two team members. When the two team members did not agree on inclusion or exclusion of an article, they met to discuss and reach consensus, and then the article was either included or excluded accordingly. In cases of when consensus was not reached by the two initial reviewers, a senior investigator reviewed the article and adjudicated the decision on inclusion or exclusion.

Data Extraction

Data from included studies were extracted into evidence tables and entered into electronic databases using Microsoft Excel® and DistillerSR systematic review software. The data extracted into evidence tables included: study design; year, setting, duration, study inclusion, and exclusion criteria; population and clinical characteristics (including sex, age, ethnicity, comorbidities, functional ability, and ulcer stage); intervention characteristics; results for each outcome of interest; and withdrawals due to adverse events. Outcomes of interest for effectiveness were: resolution of ulcer determined by complete wound healing, healing time, reduction in wound surface area, and reduction in pain, prevention of serious complications of infection such as sepsis or osteomyelitis, and ulcer recurrence rates. Outcomes of interest for harms were: pain, dermatologic reactions, bleeding, and complications including but not limited to infection and need for surgical intervention. Data on settings included patient-care settings such long term care or nursing facilities, hospital, and community. If available, we also extracted the number of patients randomized relative to the number of patients enrolled, how similar those patients were to the target population, and the funding source. We recorded intention-to-treat results when available. All summary measure data was collected as available and presented in the individual studies, including but not limited to, percentage of complete wound healing, relative risk and risk ratios, confidence intervals, and significance values. A second team member verified all study data extraction for accuracy and completeness.

One of the challenges in extracting data from PU studies is that various systems have been used to assess the severity of pressure ulcers. Most use a four-stage categorization with higher numbers indicating higher severity.[7] In 2007 the United States National Pressure Ulcer Advisory Panel (NPUAP) redefined their four-stage classification system that defines the pressure ulcer based on depth and tissue involvement. Stage I is defined as superficial erythema, stage II as partial thickness ulceration, stage III as full thickness ulceration, and stage IV as full thickness with involvement of muscle and bone. A corresponding four stage classification system was similarly adopted by the European panel and this has now taken precedence for categorizing

pressure ulcers. Given that the stages are based on depth and tissue involvement, when an ulcer has overlying purulent material or eschar prohibiting the ability to determine the depth or extent of tissue involvement, the ulcer is classified as unstageable, or stage X. A description of the most commonly used systems to classify pressure ulcers prior to adapting the NPUAP system is reviewed in Appendix C and aligned with the current corresponding NPUAP stage.

In order to allow comparability across studies, we extracted the stage or grade reported, but used the corresponding NPUAP stage in summary tables and text when possible.

Quality Assessment of Individual Studies

In this report, risk of bias is denoted as quality, with the following summary categories:

- Good quality is defined as a low risk of bias.
- Fair quality is defined as a moderate risk of bias.
- Poor quality is defined as a high risk of bias.

We used predefined criteria to assess the quality of controlled trials and observational studies at the individual study level. We also adapted criteria from methods proposed by Downs and Black[8, 9] (observational studies) and methods developed by the U.S. Preventive Services Task Force.[10]

We rated the quality of each controlled trial based on the methods described in the published reports about randomization and allocation concealment; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intention-to-treat analysis; and ascertainment of outcomes.[9] Individual studies were rated as "good," "fair," or "poor". Studies rated "good" have the least risk of bias, and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" do not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as they are to reflect the true differences between the interventions that were compared. We did not exclude studies rated poor quality *a priori*, but poor-quality studies were considered to be less valid than higher-quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Data Synthesis

Due to the heterogeneity of outcomes reported, variation in the comparators to which interventions were compared, and the limited number and quality of studies for specific

treatment comparisons, quantitative analysis was not appropriate for most bodies of literature included in this review. For most comparisons, we therefore synthesized data qualitatively.

We evaluated the appropriateness of meta-analysis based on clinical and methodological diversity of studies and statistical heterogeneity. We conducted meta-analysis in selected instances for comparisons examining the outcome of complete wound healing, where the number, quality, and homogeneity of studies permitted. We chose to limit meta-analysis to the outcome of complete wound healing because of: a) wide variability in the measurement of other outcomes including wound size reduction, and b) indication from our TEP that complete wound healing was the principal health outcome of interest. When meta-analysis was conducted, we used relative risk as the effect measure. We assessed the presence of statistical heterogeneity among the studies using standard χ^2 tests, and the magnitude of heterogeneity using the I^2 statistic.[11] We used random effects models to account for variation among studies,[12] and fixed effects Mantel-Haenszel models when variation among studies was estimated to be zero. Sensitivity analysis was conducted to assess the impact of quality on combined estimates and meta-regression was conducted to assess the association of effect measure with study duration. However, exploration of heterogeneity was typically limited by the small number of studies for each treatment category. All quantitative analyses were performed using STATA 11.0® (StataCorp, College Station, Texas, 2011).

Strength of the Body of Evidence

Within each key question, we graded the strength of evidence for effectiveness by intervention/comparator pair, and for harms by intervention, using an approach adapted from the AHRQ Methods Guide for Comparative Effectiveness Reviews. Our approach considers four major categories to rate the strength of evidence:

- Quality of studies (good, fair, poor)
- Consistency (low, moderate, or high)
- Directness (direct or indirect)
- Precision (low, moderate, or high).

As with our ratings of individual study quality, we used the terms "quality" in lieu of "risk of bias" in rating the overall strength of evidence of a given finding, with good quality defined as low risk of bias. Fair quality defined as moderate risk of bias, and poor quality defined as a high risk of bias. Our ratings for consistency and precision were trichotomous (low, moderate, high) rather than dichotomous (consistent vs. inconsistent, precise vs. imprecise), to allow for a more graded assessment of those domains.

We did not incorporate the domain of "dose-response association" into our strength of evidence ratings because few if any studies in our review included varying levels of exposure. We also did not include the domain of "plausible confounding that would decrease observed effect," because this domain is relevant primarily for observational studies, and nearly all of our findings were based on the results of clinical trials. The domain of "strength of association" is likewise relevant primarily for observational studies, where unmeasured confounders might reduce the strength of an observed association. We did give greater weight to studies demonstrating an effect on complete wound healing, as opposed to wound size reduction, based

on input from our TEP that complete wound healing represents the principal outcome of interest in pressure ulcer treatment.

We were not able to assess publication bias using a quantitative approach for most treatments, since in most cases we were not able to perform a formal pooled analysis due to the heterogeneity of interventions, comparators, or outcomes, or due to the poor quality of studies. We did attempt to evaluate the possibility of publication bias by qualitatively examining the directionality of study findings by sample size for a given intervention, and by looking for unpublished studies through our grey literature search.

The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient— Evidence either is unavailable or does not permit a conclusion..

Applicability

Applicability is an indicator of the extent to which research included in a review might be useful for informing clinical and/or policy decisions. Applicability depends on the particular question and the needs of the user of the review. Because it depends on context, there is no generally accepted universal rating system for applicability. We described features of the included studies that are relevant to applicability in terms of the elements of PICOTS (populations, interventions, comparators, outcomes, timing and settings). These elements are the features embedded in the key questions that inform clinical decision making and the degree to which the evidence is likely to pertain to the subpopulations. For example, it is important to determine whether techniques described in studies are representative of current practice. We based our approach on the guidance described by Atkins, et al.[9, 13]

Peer Review

Experts in prevention and management of pressure ulcers, geriatric medicine, wound care research, and epidemiology, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ task order officer and a designated EPC associate editor will also provide comments and editorial review. To obtain public comment, the draft report will be posted on the AHRQ Web site for 4 weeks. After addressing the public and peer review comments, a disposition of comments report detailing the changes will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

The result of the search and study selection is summarized in the study flow diagram (Figure 4 of the main report). Searches of databases, reviewing reference lists of published studies, and

review of grey literature in resulted in 6,463 potentially relevant articles. After dual review of abstracts and titles selected for full text review, and 165 full text articles were included in this review.

Overall Effectiveness of Pressure Ulcer Treatment

Pressure ulcer treatment encompasses numerous intervention strategies: alleviating the conditions contributing to ulcer development (support surfaces, repositioning, nutritional support); protecting the wound from contamination, creating a clean wound environment, and promoting tissue healing (local wound applications, debridement, wound cleansing, various adjunctive therapies); and surgically repairing the wound. We evaluated evidence addressing the comparative effectiveness and harms in treatment categories where significant uncertainty exists about the best therapeutic options. Results for each key question are presented here, within these specific treatment categories: support surfaces, nutrition, local wound applications (including wound dressings, topical therapies and biological agents), surgical interventions, and adjunctive therapies. The overall findings of this review and a summary of the strength of the evidence for the key findings are presented in Table A.

Table A. Summary of evidence: Pressure ulcer treatment strategies

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?		
Key Outcomes: Support		
Air-fluidized beds	Moderate	Five studies that involved comparing air-fluidized beds to other surfaces all reported better healing in terms of reduction in PU size or stage on air-fluidized beds.
Alternating pressure (AP) beds	Moderate	There was no evidence of differences in healing reduction in ulcer size across different brands and types of alternating pressure beds (four studies).
Alternating pressure (AP) beds compared with other surfaces	Insufficient	Two studies of alternating pressure chair cushions were conducted in two very different populations (younger people with spinal cord injury and older hospital patients or nursing home residents) and produced conflicting results, that may be due to differences in the populations (three studies).

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Alternating pressure (AP) chair cushions	Insufficient	Two studies of alternating pressure chair cushions were conducted in two very different populations (younger people with spinal cord injury and older hospital patients or nursing home residents) and produced different results, making it difficult to draw a generalizable conclusion about AP chair cushions.
Low-Air loss (LAL) beds	Moderate	There was no evidence of differences in outcomes with LAL beds compared with foam surfaces (3 of 4 studies), or with LAL beds compared with LAL overlays.
Other support surfaces	Insufficient	Four studies of surfaces presented as innovative and/or more cost effective involved different experimental surfaces and therefore we could not draw conclusions..
Key Outcomes: Nutrition		
Mixed nutritional supplementation	Low	The study quality was generally low across studies of mixed nutritional supplementation, Studies reported small benefits in the reduction of wound size and reduced healing time, but there was no evidence of benefit in terms of complete wound healing.
Protein or amino acid supplementation	Low	Healing and reduction in ulcer size were similar to slightly better among patients receiving high protein, amino acids or amino acid precursors compared to standard care, placebo or other forms of supplementation.
Specific nutrient supplementation	Insufficient	The evidence about the effectiveness and the results of either vitamin C or zinc supplementation to enhance wound healing is inconclusive. Only two studies evaluated specific nutrient supplementation without overall additional nutritional support. One was a trial of the effect of high and low doses of ascorbic acid (vitamin C) that found no significant difference in wound healing, and the other was an observational study of zinc supplementation.
Key Outcomes: Local Wound Applications		
Hydrocolloid dressings compared with Conventional Care	Low	Wound healing was superior with hydrocolloid compared with gauze dressings (10 studies).
Hydrocolloid compared with foam	Moderate	Wound healing outcomes were similar with hydrocolloid and foam dressings (seven studies, pooled RR 1.10, 95% CI 0.85 to 1.42, I^2=25.4%, p = 0.235).
Comparisons of different wound dressings	Insufficient	Evidence regarding the comparative effectiveness of hydrogel, transparent film, silicone, alginate, and gauze dressings was insufficient to draw conclusions.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Radiant heat compared with other dressings	Moderate	Radiant heat dressings produced more rapid wound healing than other dressings, but there was no evidence of benefit in terms of complete wound healing (pooled RR 1.23, 95% CI 0.70 to 2.14, I^2 = 0.0% p =0.916).
Debriding enzymes compared with dressings or other topical therapies	Insufficient	There is insufficient evidence about the effectiveness of collagenase and other debriding enzymes in improving wound healing (five studies).
Dextranomer paste compared to wound dressings	Low	Dextranomer paste is inferior to wound dressings (alginate, hydrogel) in promoting wound area reduction
Topical collagen compared with hydrocolloid dressings or standard care	Low	Wound healing was similar with topical collagen compared with hydrocolloid dressings or standard care.
Topical Phenytoin	Insufficient	Three studies of the effectiveness of topical phenytoin used different comparators and produced inconsistent results.
Platelet-derived growth factor	Low	Platelet-derived growth factor was superior to placebo in the healing of stage III and IV pressure ulcers (three studies, strength of evidence: low).
Biological Agents other than platelet-derived growth factor	Insufficient	There was insufficient evidence about the effectiveness of other biological agents used for the treatment of pressure ulcers.
Key Outcomes: Surgery		
Sacral compared to Ischial pressure ulcers	Low	Sacral pressure ulcers have lower recurrence rates after surgery than ischial pressure ulcers
Key Outcomes: Adjunctive		
Electrical stimulation	Moderate	Electrical stimulation was beneficial in the rate of healing of stage II, III, and IV pressure ulcers based on one good-quality and eight fair-quality randomized trials.
Electrical stimulation	Insufficient	Evidence about the effect of electrical stimulation on complete wound healing of stage II, III, and IV pressure ulcers was inconclusive, due to heterogeneous results from six randomized trials.
Electromagnetic therapy	Low	There was no evidence of benefit with electromagnetic therapy in wound healing of stage II, III, or IV pressure ulcers in patients based on three randomized trials and one systematic review.
Therapeutic ultrasound	Low	There was no evidence of benefit with ultrasound in terms of complete wound healing based on one systematic review of two randomized trials.
Negative pressure wound therapy	Low	There was no evidence of benefit with negative pressure wound therapy in wound healing over 4 to 6 weeks of therapy based on two randomized trials and one observational study.
Light therapy	Low	There was no evidence of benefit with light therapy in complete wound healing based on two randomized trials.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Light therapy	Low	Light therapy may be beneficial in reducing wound surface area over time compared with standard care or sham light therapy based on five randomized trials.
Laser therapy	Low	There was no evidence of benefit with laser therapy in wound healing based on four randomized trials.
Question 1a: Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?		
Support		
	Insufficient	Most of the studies of support surfaces identified for this review did not include any subgroup analyses.
Nutrition		
	Insufficient	Only 3 of the 15 studies analyzed results by PU characteristics and the impact on the conclusion was inconsistent.
Local Wound Applications		
	Insufficient	Few studies conducted subgroup analyses by ulcer characteristics.
Surgery		
	Insufficient	No studies.
Adjunctive		
	Insufficient	
Question 1b: Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including but not limited to: age; race/ethnicity; body weight; specific medical comorbidities; and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?		
Key Outcomes: Support		
	Insufficient	Few studies presented any subgroup analyses making it impossible to draw any conclusions about the impact of patient characteristics on the effectiveness of different support surfaces in PU healing.
Key Outcomes: Nutrition		
	Insufficient	No studies

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Key Outcomes: Local Wound Applications		
	Insufficient	Indirect comparisons across studies to evaluate the possibility that treatment effectiveness is modified by ulcer or patient characteristics are limited by the fact that there were relatively few studies evaluating any given treatment comparison and by the fact that aside from ulcer stage and location, patient age and gender, few variables were reported consistently across studies.
Key Outcomes: Surgery		
	Low	Spinal cord injured patients appeared to be at greater risk of recurrent pressure ulcer after surgical flap than other patients with pressure ulcers.
Key Outcomes: Adjunctive		
Electromagnetic therapy *Therapeutic ultrasound* *Negative pressure wound therapy* *Light therapy* *Laser therapy*	Insufficient	Insufficient evidence to determine if the effectiveness of electromagnetic therapy compared with sham EMT; ultrasound therapy compared with sham US; negative pressure wound therapy; light therapy; or laser therapy varied based on features of the pressure ulcers, characteristics of the patient.
Question 1c: Does the comparative effectiveness of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?		
Key Outcomes: Support		
	Insufficient	Few studies presented any subgroup analyses making it impossible to draw any conclusions about the impact of patient care settings on the effectiveness of different support surfaces in PU healing.
Key Outcomes: Nutrition		
	Insufficient	No studies

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Key Outcomes: Local Wound Applications		
	Insufficient	Indirect comparisons across studies to evaluate the possibility that treatment effectiveness is modified by patient care setting characteristics are limited by the fact that there were relatively few studies evaluating any given treatment comparison by study setting, and that few variables were reported consistently across studies.
Surgery		
	Insufficient	No studies.
Key Outcomes: Adjunctive		
Electromagnetic therapy *Therapeutic ultrasound* *Negative pressure wound therapy* *Light therapy* *Laser therapy*	Insufficient	Insufficient evidence to determine if the effectiveness of electromagnetic therapy compared with sham EMT; ultrasound therapy compared with sham US; negative pressure wound therapy; light therapy; or laser therapy varied based on features of the patient care settings.
Question 2: What are the harms of treatments for pressure ulcers?		
Harms: Support		
	Insufficient	Few of the identified studies (7 out of 22) explicitly addressed harms attributable to support surfaces. In those where harms are mentioned, most reported no significant differences in harms across the different support surfaces.
Harms: Nutrition		
	Insufficient	Harms or adverse events were reported in about half of the studies (8 of 15), but they reported different harms, did not allow describe the harm, or did not specify if it was related to treatment.
Harms: Local Wound Applications		
Dressings and topical therapies	Moderate	Harms reported with dressings and topical therapies for pressure ulcers most commonly included skin irritation and inflammation and tissue damage and maceration. Variability in study populations, interventions, adverse event measurement, and reporting precluded an estimate of adverse event rates for dressings and topical therapies.
Dressings and topical therapies	Insufficient	There was insufficient evidence as to whether specific dressing types or topical therapies are associated with fewer harms than others (seven studies).
Biologic agents	Insufficient	Few harms were reported with biological agents. There was insufficient evidence about differences in the effectiveness or harms of wound dressings, topical treatments, or biological agents according to ulcer, patient, or setting characteristics.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Harms: Surgery		
	Low	Reoperation due to recurrence or flap failure ranged from 12 to 24 percent.
Harms: Adjunctive		
Electrical stimulation	Low	The most common adverse effect of electrical stimulation was local skin irritation.
Electromagnetic therapy *Therapeutic ultrasound* *Negative pressure wound therapy*	Insufficient	There is insufficient evidence about the harms of electromagnetic therapy, ultrasound, and negative pressure wound therapy
Light therapy	Low	Light therapy was not associated with significant adverse events based on four randomized studies
Laser therapy	Low	Short-term use of laser therapy was not associated with significant adverse events or overall withdrawal based on three randomized studies
Question 2a: Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?		
Harms: Support		
	Insufficient	No studies
Harms: Nutrition		
	Insufficient	No studies
Harms: Local Wound Applications		
	Insufficient	No studies reported subgroup analyses to evaluate harms by ulcer, patient, or setting characteristics.
Harms: Surgery		
	Low	Wound dehiscence is more common if bone is removed at time of surgical procedure.
	Low	Ischial sites are associated with greater complications than sacral or trochanteric sites
Harms: Adjunctive		
	Insufficient	There was insufficient evidence to determine if differences in harms of any adjunctive therapies exist based on features of the pressure ulcers
Question 2b: Do the harms of treatment strategies differ according to patient characteristics, including: age, race/ethnicity; body weight; specific medical comorbidities; and knows risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?		

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Harms: Support		
	Insufficient	No studies
Harms: Nutrition		
	Insufficient	No studies
Harms: Local Wound Applications		
	Insufficient	No studies
Harms: Surgery		
	Insufficient	No studies
Harms: Adjunctive		
Electrical stimulation	Low	Frail elderly patients experience more adverse events with electrical stimulation compared with a younger population.
Question 2c: Do the harms of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?		
Harms: Support		
	Insufficient	No studies
Harms: Nutrition		
	Insufficient	No studies
Harms: Local Wound Applications		
	Insufficient	No studies
Harms: Surgery		
	Insufficient	No studies
Harms: Adjunctive		
	Insufficient	There was insufficient evidence to determine if differences existed in harms based on patient care setting or features of the patient care setting.

Note: PU, pressure ulcer.

Discussion

Treatment for pressure ulcers involves a variety of different modalities intended to: alleviate the conditions contributing to ulcer development (support surfaces, repositioning, nutritional support); protect the wound from contamination, create a clean wound environment, and promote tissue healing (local wound applications, debridement, wound cleansing, and a variety of adjunctive therapies); and surgically repair the wound. We evaluated evidence addressing the

comparative effectiveness and harms in treatment categories where significant uncertainty exists about the best therapeutic options: support surfaces, nutritional supplements, local wound applications (dressings, topical therapies, biological agents), surgical interventions, and adjunctive therapies. We also attempted to discern whether the balance of benefits and harms for different treatment options varied according to characteristics of the pressure ulcer, the patient, or the setting in which care was being delivered.

Key Findings and Strength of Evidence

We identified evidence addressing a variety of different support surfaces, including air-fluidized beds, alternating pressure beds and chair cushions, and low air-loss beds. Other types of support surfaces were evaluated only in small, single studies. We found evidence of moderate strength that air-fluidized beds are superior to other support surfaces. Evidence about the effectiveness of alternating pressure surfaces was inconclusive, though among alternating pressure beds, we found moderate-strength evidence that different mattress brands performed similarly. There was moderate-strength evidence that low air-loss beds do not convey benefit over standard foam mattresses. The harms of different support surface options were minimal.

Studies of nutritional support evaluated increased mixed nutritional supplementation including increased caloric intake and vitamins with or without high protein supplementation, protein or amino acid supplementation using protein or amino acids with or without additional caloric support or vitamin supplementation, and specific nutrient supplementation with vitamins or minerals such as ascorbic acid (vitamin C) or zinc. Studies provided low strength of evidence for a small benefit in wound size reduction and healing time with mixed nutritional supplementation. There was also low strength of evidence indicating no or small benefits in wound healing with protein or amino acid supplementation. Evidence about vitamin supplementation alone was insufficient to draw conclusions.

A wide variety of modern wound dressings have been compared to each other or to standard care, usually with gauze dressings. We found low-strength evidence that hydrocolloid dressings are superior to gauze and moderate-strength evidence that hydrocolloid and foam (hydrocellular or polyurethane) dressings produced similar wound healing results. Evidence about the comparative effectiveness of other dressings – hydrogels, transparent films, silicone, and alginates – was insufficient to draw conclusions. We found moderate-strength evidence from four studies that radiant heat dressings accelerated the rate healing compared to other dressings, but we did not find evidence of a benefit of radiant heat dressings in terms of complete wound healing.

The most commonly evaluated topical therapies were debriding enzymes (primarily collagenase), phenytoin solution, dextranomer paste, and collagen. There was low-strength evidence that dextranomer is less effective than standard wound dressings or other topical agents. Evidence about enzymes and phenytoin was inconsistent, and insufficient to draw conclusions. Collagen did not appear to provide wound healing benefit compared to standard care, based on low-strength evidence.

The most commonly evaluated biological agent was platelet-derived growth factor (PDGF), for which there was low-strength evidence of benefit compared to placebo in promoting healing of severe (stage III or IV) ulcers. There was insufficient evidence about the effectiveness of other biological agents.

There was moderate-strength evidence that the most common harms of wound dressings and topical agents were dermatologic complications, including irritation, inflammation, and maceration. However, variability across studies precluded an estimate of adverse events for specific dressings or topical therapies, and evidence was insufficient to determine whether certain types of dressings or topical therapies were more likely to cause these complications than others. Few harms were reported with biological agents, but the evidence about the harms of these agents was insufficient to reach conclusions about adverse event rates. Evidence was insufficient to make conclusions about the effectiveness or harms of local wound applications across different ulcer or patient characteristics, or settings.

Surgical interventions for pressure ulcers identified in studies meeting our inclusion criteria were primarily surgical flaps, most commonly myocutaneous and fasciocutaneous flaps. Studies of surgical interventions were nearly all observational, and most were conducted in single centers. All findings related to the comparative effectiveness and harms of surgical interventions were considered low strength. These findings included a lower rate of ulcer recurrence with sacral ulcers compared to ischial ulcers; a higher rate of recurrent ulcer among patients with spinal cord injury compared with others; greater wound dehiscence rates with myocutaneous compared to fasciocutaneous flaps and with surgeries in which bone is removed as part of the operation; and more adverse events with surgery for ischial compared to sacral or trochanteric ulcers. Surgical flap failures requiring reoperation ranged from 12 to 24 percent.

Adjunctive therapies identified in our review included electrical stimulation, electromagnetic therapy, ultrasound, negative pressure wound therapy, light therapy, and laser therapy. Evidence about other adjunctive therapies – including nonthermic therapy, hydrotherapy, vibration, shock wave, and hyperbaric oxygen – was limited to small, single studies. There was moderate-strength evidence that electrical stimulation improved healing rates, but inconclusive evidence about the effect of electrical stimulation on complete wound healing due to heterogeneous findings across studies. Low-strength evidence indicated that the most common adverse effect of electrical stimulation was local skin irritation; and that harms were more common in frail elderly compared to younger populations. There was also low-strength evidence indicating that electromagnetic therapy, therapeutic ultrasound, and negative pressure wound therapy were similar to sham treatment or standard care in wound healing outcomes; there was insufficient evidence to evaluate the harms of those adjunctive therapies. Light therapy provided benefit in terms of wound area reduction but not complete wound healing, and was not associated with significant adverse events, based on low-strength evidence. There was low-strength evidence that laser therapy was not associated with significant adverse events, but also that it did not provide wound healing benefit over sham or standard treatment.

Findings in Relationship to What is Already Known

The most current, comprehensive evidence about the effectiveness of pressure ulcer treatments comes from a systematic review by Reddy et al., published in December 2008, that evaluated 103 randomized trials published during or prior to August 2008.[7] The review included studies evaluating support surfaces, nutritional supplements, wound dressings, biological agents, and adjunctive therapies. Our review included evaluations of those treatment categories and additionally evaluated surgical interventions, included observational studies of pressure ulcer treatments, and assessed treatment harms, in studies published through September 14, 2012.

The findings of this prior systematic review were qualitatively similar to ours, with a few exceptions. In the support surface category, Reddy et al. reported that alternating pressure surfaces and low air-loss beds were not superior to standard, non-powered surfaces. They did not, however, report specifically on air-fluidized beds, and only one of the 5 studies of AF beds included in our review were retrieved in their literature search. Our finding that there was moderate-strength evidence that AF beds were more effective than other surfaces in achieving wound area reduction has not, to our knowledge, been reported in prior reviews.

Reddy et al. reported that overall, nutritional supplements did not provide benefit in terms of ulcer healing, but that protein supplementation may provide benefit. Our findings were similar; we found suggestive evidence that mixed nutritional and protein supplementation may provide wound healing benefit, but this conclusion was supported a low strength of evidence.

Our findings with regard to wound dressings and topical therapies, indicating that there was limited evidence to support the use of certain dressings and topical therapies over others, were similar to the conclusions drawn by Reddy et al. They highlighted a study demonstrating the superiority of alginate dressings to dextranomer paste; we also found dextranomer paste to be inferior to dressing but considered the evidence for this to be low-strength. We did find moderate-strength evidence that radiant heat dressings accelerated the rate of wound area reduction, but we did not find evidence of a benefit of radiant heat dressings in terms of complete wound healing. Similar to Reddy et al., we found a potential benefit, based on low-strength evidence, for platelet-derived growth in promoting healing with stage III and IV ulcers.

Our findings for adjunctive therapies were likewise similar to those of Reddy et al. We found low-strength or insufficient evidence for most adjunctive therapies, limiting the ability to make conclusions about the effectiveness and harms of those treatments. The review by Reddy et al. was also similar to ours in its assessment that the overall quality of the literature evaluating pressure ulcer treatments was poor.

Applicability

The applicability of our findings to real-world clinical settings is supported by several features of the body of literature we reviewed. First, the populations studied included a broad representation of patients with pressure ulcers – elderly patients, general populations of patients with limited mobility, patients with spinal cord injury – cared for in a wide variety of settings, including hospitals, nursing homes, wound care clinics, and at home. Second, the interventions represented most of the therapeutic modalities commonly used in clinical settings. Comparators were also commonly used therapies and often included standard care as defined by local practice patterns.

Other features of the studies we identified, however, limit the applicability of our findings. First, the outcome in many studies was wound size (area, volume, or depth) reduction, as opposed to complete wound healing. Although wound size reduction is a reasonable measure of therapeutic effect, in clinical practice the goal of therapy is almost always complete wound healing, making wound size reduction a surrogate outcome with less clinical significance than complete wound healing. A principal reason for findings of wound size reduction without complete wound healing was the short duration of most trials. Complete healing takes time, and interventions lasting only a few weeks, as was the case for many if not most of the trials included

in our review, are less likely to achieve complete wound healing than interventions carried out for periods long enough for complete healing to occur, as they would be in clinical practice.[b]

Studies of surgery are additionally limited by the fact that most were observational and conducted in one or, at most, a few centers. Because surgical technique and quality is often operator- and/or site-dependent, and because outcomes are influenced by local practices, staffing, and other features of the environment, it is difficult to generalize the findings of studies of surgery included in this review.

Implications for Clinical and Policy Decisionmaking

The limitations in applicability discussed above, as well as the limitations of the evidence base discussed below, make it difficult to draw firm conclusions with implications for clinical and policy decisionmaking. Notably, we generated no findings that were supported by a high strength of evidence, and only a few findings supported by moderate-strength evidence. Most findings were based on low-strength evidence, and for many issues there was insufficient evidence to draw any conclusions.

The finding that air-fluidized beds are superior to others might warrant consideration of greater investment in this technology. However, any decisions about such investments would need to take into account both the fact that the effectiveness of these beds was measured in terms of wound size reduction, rather than complete wound healing, and the cost associated with this technology compared to other surfaces.

Nutritional supplementation may provide benefit in terms of wound healing, though the effects of nutritional supplementation were not dramatic, and it was not clear from the studies in our review whether nutritional supplementation was beneficial to all patients or to those with evidence of nutritional deficiencies. Nutritional support is commonly prescribed for ill or debilitated patients with evidence of malnutrition; whether this affects ulcer healing, and whether patients without evidence of malnutrition might benefit from nutritional supplementation, is not clear.

Decisions about dressings and topical applications are often guided by matching the primary functions of different dressings (e.g., absorbent, hydrating) with the primary considerations for treatment of individual ulcers (e.g., dryness, contamination risk, exudate). Given the wide array of options, comparative effectiveness and harms data has great potential to guide individualized decisionmaking. We found limited evidence, however, to provide such guidance. Overall, we did not find substantial evidence to support certain local wound applications over others. There was evidence to suggest that radiant heat improved the pace of wound healing, but not complete wound healing per se. Some biological agents showed promise for the treatment of severe ulcers, but the evidence was not substantial, and in light of the cost of these agents, more and better evidence is likely needed before they are widely adopted.

Surgery is typically reserved for refractory ulcers unlikely to heal with conservative management. Evidence about surgery is limited to mainly single-center observational studies. While we found some evidence to inform decisions and expectations about which ulcers will fare

[b] Secondly, the treatment of pressure ulcers in clinical practice often involves multiple concurrent therapies such as support surfaces, nutritional supplementation, biologic or topical therapies, and adjunctive interventions. No studies compared one combination of concurrent or sequential therapies to another and no conclusions can be drawn regarding the effectiveness of one compared to another.

best with surgical intervention, and which surgeries are likely to produce the lowest complication rates, the influence of those findings on clinical decisionmaking should be tempered by the low quality of the studies that produced the findings, and the potentially limited generalizability of the findings across sites and surgeons.

Adjunctive therapies include therapies that are variably used in the treatment of pressure ulcers. Our review revealed moderate-strength evidence that electrical stimulation may accelerate healing but did not otherwise produce findings that would support greater use of adjunctive therapies.

Limitations of the Comparative Effectiveness Review Process

The most important potential limitations of the of our review process are that we did not identify important studies whose findings might influence clinical and policy decisionmaking, and potential bias either in the conduct of the identified studies or in our evaluation of evidence from those studies. The two main threats to incomplete identification of evidence are an inadequate literature search, and biased reporting of results such that only selected studies were published and retrievable. To overcome these potential limitations, we conducted a comprehensive, broadly inclusive search that produced 6463 study titles and abstracts. Although we excluded studies published before 1985, we do not believe that important studies of therapies used in current practice were missed; the general consistency of our findings with the systematic review by Reddy et al., which included pre-1985 studies, provides some assurance that our review was not biased by our time frame selection.

Reporting bias is a concern in any systematic review. We were not able to conduct quantitative analyses to evaluate the possibility of reporting bias for most of our findings because the heterogeneity across studies in our review generally precluded meaningful comparison of effect sizes. Mitigating against the likelihood of reporting bias in our review, however, is the fact that the majority of studies in our review were small (most fewer than 100 patients, many fewer than 50), and most reported no significant effect of the intervention. Reporting bias typically results in selective publication of larger studies and/or those with positive findings. We also conducted grey literature searches to look for unpublished data and did not find evidence of unreported studies.

We took several measures to guard against the influence of bias in the identified studies, or in our evaluation of those studies. Abstracts were reviewed by at least two team members, including a clinician/senior investigator. Studies were extracted based on prespecified data elements, extraction done by one team member was checked by another, and quality rating of studies was performed by two team members and disagreements adjudicated by consensus. Rating of elements of strength of evidence was discussed and calibrated among team members.

Limitations of the Evidence Base

The main limitation of the evidence base in our review was poor study quality. Most trials did not specify randomization method, did not conceal allocation, and did not mask outcomes assessment. Most studies did use intention-to-treat analyses. Most studies were small, and many were underpowered to detect significant differences. Studies were also highly variable in terms of patient populations, ulcer characteristics (e.g., anatomic site, duration, stage), interventions (even within a given intervention category, e.g., different types of foam dressings), and

comparators (especially variability in implementation of standard, or usual, care), limiting our ability to combine or compare results across studies.

Another major limitation of the evidence base relates to the most common outcome measure, wound size reduction. Comparing changes in the size of PUs poses several measurement issues. For example, reduction in the size of larger and smaller PUs is hard to compare. Healing could involve "bridges" that split a large ulcer into two. Measurement in person or from tracings or photographs can be difficult, especially when measurement and photographic techniques are not standardized across studies.

Finally, a major limitation of studies in our review was the duration of interventions and followup periods. Many pressure ulcers, especially more severe ulcers, may take weeks to months to heal. Many of the studies in our review were implemented over a period that did not necessarily allow for complete ulcer healing and therefore detection of significant differences in ulcer healing across groups.

Research Gaps

The major gaps in research identified by our review relate to the limitations of the evidence base as described above. Future research with larger sample sizes, more rigorous adherence to methodological standards for clinical trials, longer followup periods, and more standardized and clinically meaningful outcome measures is needed to inform clinical practice and policy.

One clinical area identified as high-priority by our Technical Expert Panel, for which we found limited evidence, is hyperbaric oxygen therapy. Although studies, and systematic reviews, have evaluated this treatment in chronic wounds generally, its utility among patients with pressure ulcers has not been evaluated specifically.

Conclusions

We found limited evidence to draw firm conclusions about the best approaches for treating pressure ulcers. This finding is consistent with that of a recent systematic review addressing most of the same treatment categories included in our review.[7] Although we did find evidence from five studies indicating a benefit for air-fluidized beds over other support surfaces, from four studies indicating a benefit of radiant heat dressings over other dressings, and from nine studies indicating a benefit of electrical stimulation, but the benefit observed in all cases was wound size reduction or healing rates, rather than completely healed wounds. The balance of costs and potential harms of those technologies against the benefits observed is unclear.

Choices of wound dressings and topical applications are often guided by product availability, local practice patterns, and individualized decisionmaking based for specific patients and the features of a given pressure ulcer. Our review did not generate findings to guide those choices based on evidence. Studies generally did not provide evidence to support the use of one type of commonly used dressing over another. There was evidence that hydrocolloid and foam dressings performed similarly, but evidence for other dressing types – hydrogels, alginates, transparent films, silicone dressings – compared with each other or to standard gauze dressings was limited. Similarly, there was low-strength or insufficient evidence to judge the balance of effectiveness and harms for nutritional supplementation, topical therapies, biological agents, surgical interventions, and adjunctive therapies other than electrical stimulation, which appeared to

improve healing rates. Advancing pressure ulcer care will require more rigorous study to solidify the evidence base for this important and widely used set of treatments.

References

1. Bergstrom N, Bennett MA, Carlson CE, et al. Pressure Ulcer Treatment. Clin Pract Guidel Quick Ref Guide Clin. 1994;15.

2. Graves N, Birrell F, Whitby M. Effect of pressure ulcers on length of hospital stay. Infect Control Hosp Epidemiol. 2005;26(3):293-7.

3. Lyder CH. Pressure ulcer prevention and management. JAMA. 2003 Jan 8;289(2):223-6. PMID: 12517234.

4. NPUAP. Pressure Ulcer Prevention and Treatment: Clinical Practice guidline. National Pressure Ulcer Advisory Panel and European Pressure Ulcer Advisory Panel. 2009.

5. AHRQ. Methods Guide for Effectiveness and Comparative Effectiveness Reviews: Agency for Healthcare Research & Quality; 2011.

6. Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academy of Sciences; 2011.

7. Reddy M, Gill SS, Kalkar SR, et al. Treatment of pressure ulcers: a systematic review. JAMA. 2008 Dec 10;300(22):2647-62. PMID: 19066385.

8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. JECH. 1998;52(6):377-84. PMID: 9764259.

9. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID: 11306229.

10. USPSTF. U.S. Preventive Services Task Force Procedures Manual: United States PreventiveServices Task Force; 2008.

11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58. PMID: 12111919.

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.

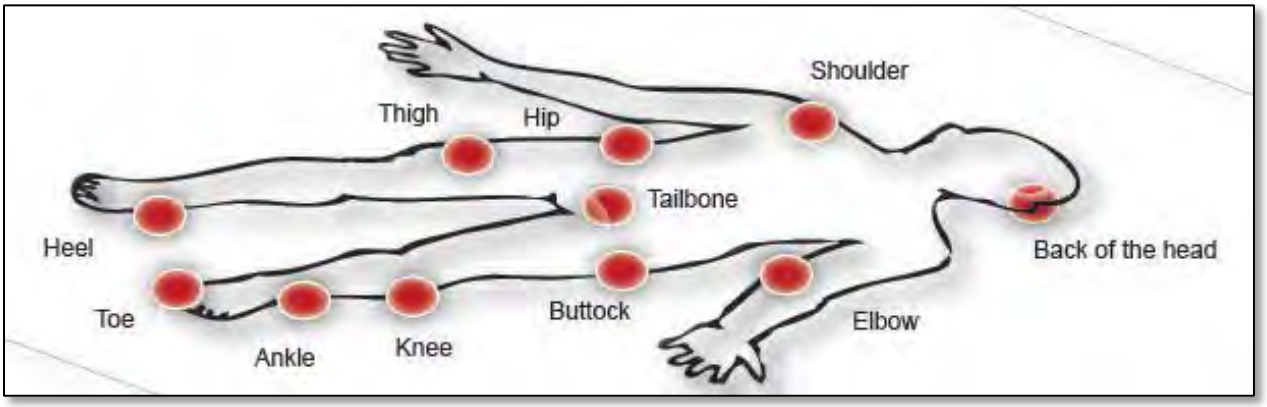
13. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207. PMID: 21463926.

Introduction

Background

Uninterrupted pressure exerted on the skin, soft tissue, muscle, and bone can lead to the development of localized ischemia, tissue inflammation, tissue anoxia, and necrosis. Pressure ulcers affectthree million adults in the United States. Common areas of the body prone to the development of pressure ulcers are depicted in Figure 1. Estimates of the incidence of pressure ulcers vary according to the setting, with ranges of 0.4 to 38.0 percent in acute-care hospitals, 2.2 to 23.9 percent in long-term nursing facilities, and 0 to 17 percent in home care.[1, 2]

Figure 1. Common pressure ulcer sites



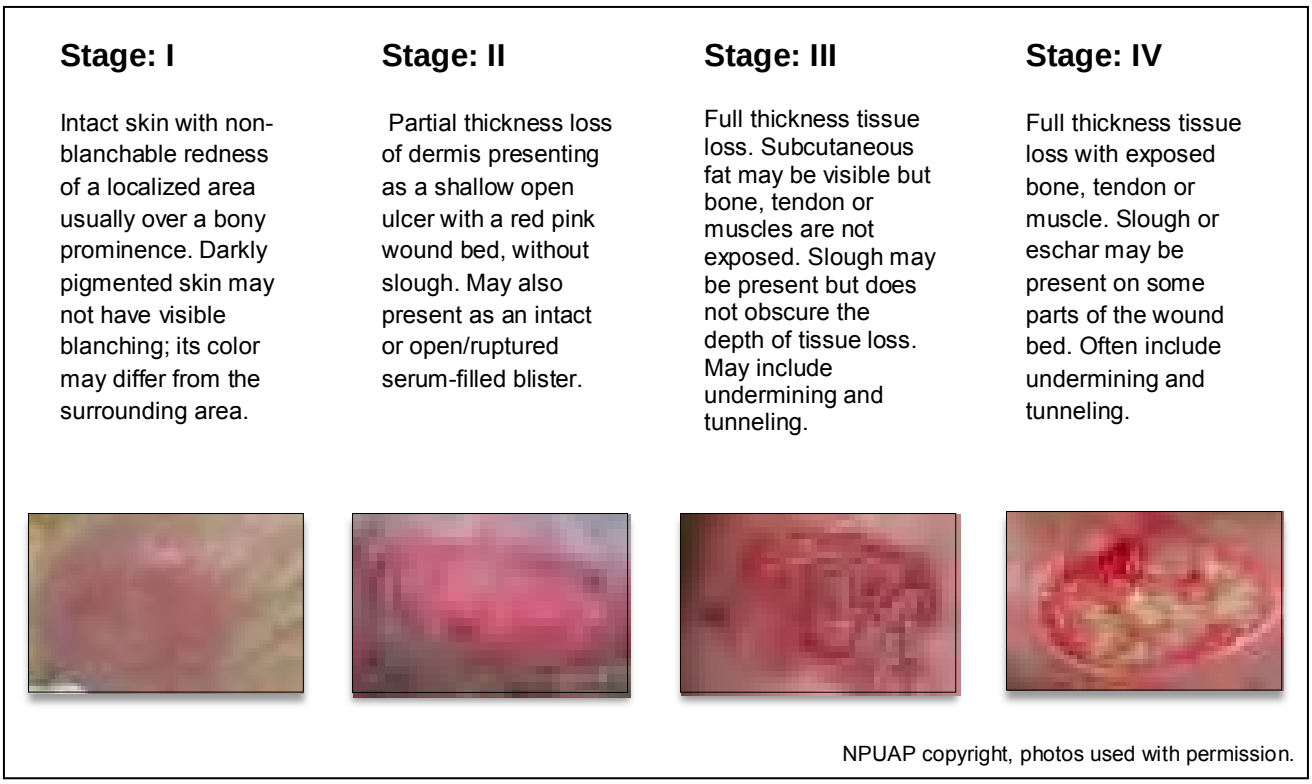
EPC

Pressure ulcer healing rates, which are dependent on comorbidities, clinical interventions, and severity of the ulcer, vary considerably. Ulcer severity is assessed using a variety of different staging or grading systems; the National Pressure Ulcer Advisory Panel (NPUAP) staging system is the most commonly used (Figure 2). Comorbidities predisposing to pressure ulcer development and affecting ulcer healing include those affecting patient mobility (e.g., spinal cord injury), wound environments (e.g., incontinence), and wound healing (e.g., diabetes, vascular disease). Delayed healing can add to the length of hospitalization and impede return to full functioning.[2] Data on the costs of treatment for a pressure ulcer vary, but some estimates range between $37,800 and $70,000, with total annual costs in the United States as high as $11 billion.[1, 3]

Given the negative impact PUs have on health status and patient quality of life, as well as health care costs, treatments are needed that promote healing, shorten healing time, minimize the risk of complications, and increase the likelihood of complete healing. Pressure ulcer treatment involves a variety of different approaches, including interventions to treat the conditions that give rise to pressure ulcers (support surfaces, nutritional support), interventions to protect and promote healing of the ulcer itself (wound dressings, topical applications, and various adjunctive therapies including vacuum-assisted closure, ultrasound therapy, electrical stimulation, and hyperbaric oxygen therapy), and surgical repair of the ulcer.[1, 3] Most ulcers are treated using a combination of these approaches. Standards of care for pressure ulcer treatment are typically guided by clinical practice guidelines, such as those developed by the NPUAP, but also vary by patient-related factors such as comorbidities and nutritional status,[4] local practice patterns, and the stage and features of the wound. Current guidelines primarily reflect expert opinions. An

examination of the comparative effectiveness and harms of the wide variety of different therapies and approaches to treating pressure ulcers is important to guide clinical practice.

Figure 2. National Pressure Ulcer Advisory Panel pressure ulcer stages



Scope and Key Questions

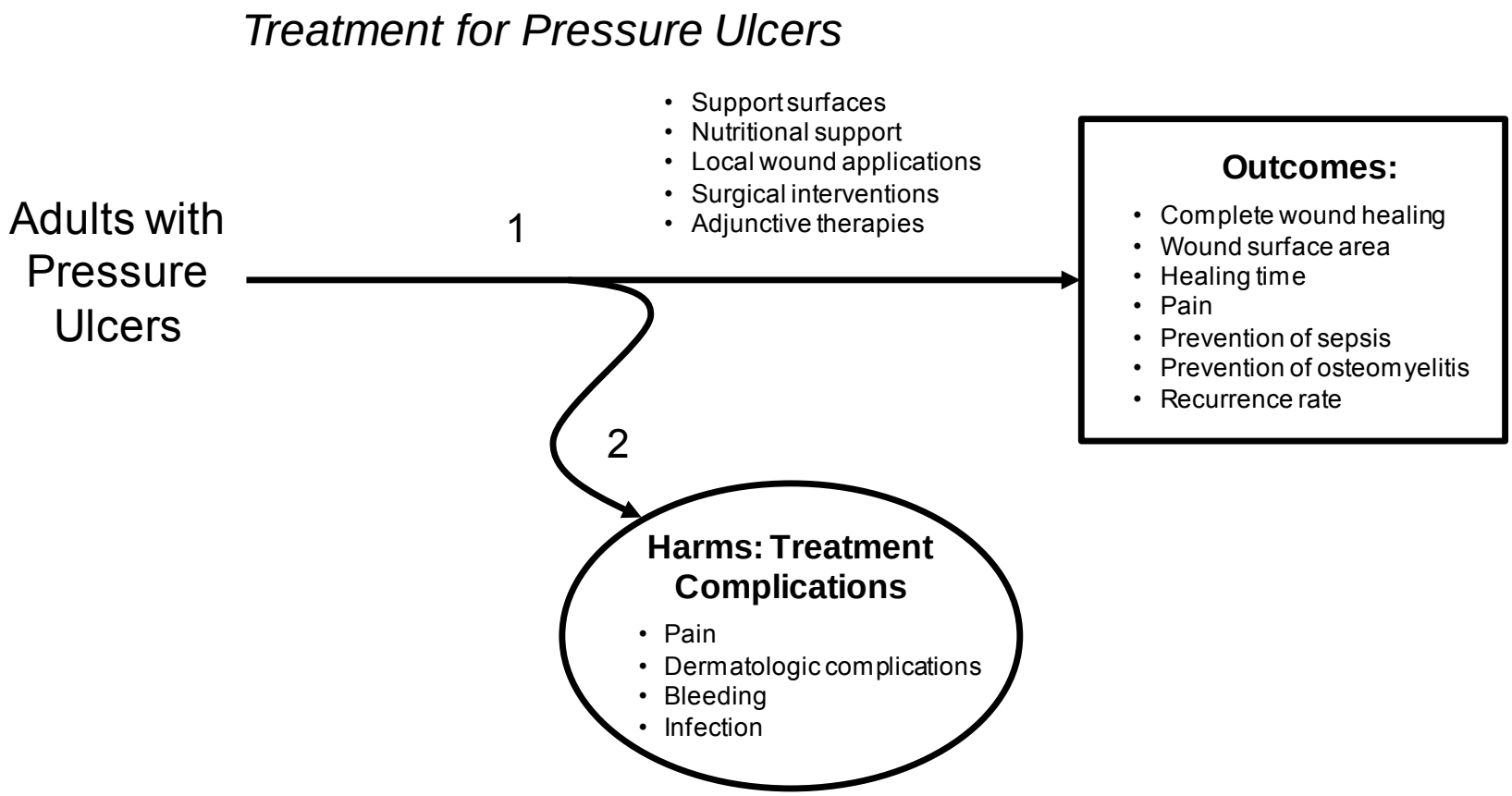
This topic was selected for review based on two separate nominations that also included questions related to risk assessment and prevention of pressure ulcers. This report addresses the comparative effectiveness of various pressure ulcer treatment approaches while the topic of prevention, including secondary prevention of recurrent pressure ulcers, is addressed in a companion report. Both reports are intended to serve as the foundation for the development of updated guidelines on pressure ulcer prevention and treatment.

The key questions were developed with input from key informants, including clinicians, wound care researchers, and patient advocates. The analytic framework and key questions used to guide this report are shown below (Figure 3). The analytic framework shows the target populations, interventions, outcomes and harms we evaluated.

The general categories of treatment included in this report are: support surfaces, nutritional supplements, local wound applications (including wound dressings, topical therapies, and biological agents), surgical procedures, and various adjunctive therapies. Other facets of pressure ulcer care (e.g., repositioning, non surgical wound debridement, wound cleansing) were not considered areas where comparative effectiveness evidence was likely to be found or to significantly influence clinical care. We evaluated the evidence on comparisons within the general categories (for example, comparisons between two types of dressings). We also sought direct evidence on comparisons across the general categories (for example, dressings vs. support

surfaces). However, we did not identify any head-to-head comparisons of treatments across categories. This review also included an assessment of adverse effects or harms associated with pressure ulcer treatment, such as dermatologic complications, bleeding, pain, or infection. Finally, we included an assessment of future research needs on this important clinical topic.

Figure 3. Analytic framework: Pressure ulcer treatment strategies



Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?

Key Question 1a. Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?

Key Question 1b. Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including but not limited to: age; race/ethnicity; body weight; specific medical comorbidities; and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?

Key Question 1c. Does the comparative effectiveness of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

Key Question 2. What are the harms of treatments for pressure ulcers?

Key Question 2a. Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?

Key Question 2b. Do the harms of treatment strategies differ according to patient characteristics, including: age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?

Key Question 2c. Do the harms of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

Population and Conditions of Interest

The population studied was adults ages 18 and older with a pressure ulcer. Patients with pressure ulcers usually also have limited or impaired mobility and suffer from other chronic illnesses. Pressure ulcers are most common in the elderly or people with spinal cord injuries or other conditions that restrict movement and mobility. Patients with non pressure-related ulcers, including but not limited to venous ulcers and diabetic foot ulcers, were excluded because treatment considerations for these patients may differ significantly from those for pressure ulcers. We excluded children because this topic was originally nominated and scoped for adults.[a] Key informants agreed with the broadly defined proposed population of interest as "adults with pressure ulcers." They endorsed the proposed list of included patient characteristics that should be considered, but they also noted that "adults with pressure ulcers" is a heterogeneous group

[a] Although treatment approaches for children with pressure ulcers may be similar, other factors may influence the effectiveness differently in this population, including setting, caregiver attention, healing potential and comorbidities.

and that variability in the comparative effectiveness of pressure ulcer treatments may be related to a large number of patient characteristics. In addition to sex, race/ethnicity, socioeconomic status, and diverse specific medical comorbidities (e.g., diabetes, end-stage renal disease, dementia), many informants suggested that we include specific known risk factors for pressure ulcers (e.g., nutritional status, incontinence, peripheral vascular disease, mobility limitations, functional ability). See Appendix B for detailed inclusion and exclusion criteria.

Interventions and Comparators

Various treatment strategies for pressure ulcers were addressed, including but not limited to therapies that address the underlying contributing factors (e.g., support surfaces and nutritional supplements), therapies that address local wound care (e.g., wound dressings, topical therapies, and biological agents), surgical repair, and adjunctive therapies (e.g., physical therapy).

Combined treatment modalities (cointerventions) were also evaluated (such as comparison of two treatments in combination, compared with a single treatment).

Comparators included placebo or active control, usual care, or other interventions.

Outcomes

The most commonly examined outcomes were various measures of wound healing. Some studies examined complete wound healing as the primary outcome, though many studies evaluated wound size reduction. Based on input from our TEP, we considered complete wound healing to be the principal health outcome of interest. However, we also considered wound size reduction to be an important outcome, because: a) it represents a necessary intermediate step towards the principal outcome of complete wound healing (i.e., complete wound healing can be considered 100 percent wound size reduction); b) the likelihood of complete wound healing is lower for larger or higher-stage ulcers, and therapies deployed for more advanced ulcers may not be expected to achieve complete wound healing over the course of several weeks, which was the duration of most of the studies in our review. Thus, in summarizing the evidence about a given treatment, we considered both complete wound healing and wound size reduction as part of the overall outcome of "wound healing," but we gave more weight to evidence of complete wound healing. Other outcomes included wound healing rate and time, pain, and avoidance of serious complications of infection. For harms of treatment we evaluated pain, dermatologic complications, bleeding, infection, and other adverse outcomes as reported in identified studies.

Timing

We did not apply minimum followup duration for studies.

Setting

Settings included patient care settings, such as home, nursing facility, or hospital.

Methods

The methods for this comparative effectiveness review (CER) follow the methods suggested in the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[5] and the standards suggested by the Institute of Medicine for conducting systematic reviews.[6]

Topic Refinement and Review Protocol

The key questions for this CER were developed with input from key informants, representing clinicians, wound care researchers, and patient advocates, who helped refine key questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised key questions were then posted to the AHRQ public Web site for a four-week comment period, which concluded June 9, 2011. The Agency for Healthcare Research and Quality and the EPC agreed upon the final key questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report. We then drafted a protocol for the CER, which was reviewed by the TEP and is available from the AHRQ Web site (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=838&pageaction=displayproduct).

A multidisciplinary group of clinicians, researchers, and patient advocates with expertise in pressure ulcer treatment and research was selected to serve as TEP members to provide high-level content and methodological expertise throughout the development of the review. Participants included leaders in the areas of pressure ulcer treatment and research, wound care and physical therapy, and plastic and reconstructive surgery, as well as patient safety advocacy and national pressure ulcer treatment advisory panel members.

TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the authors reviewed the disclosures and determined the panel members had no conflicts of interest that precluded participation.

Search Strategy

For the primary literature we searched MEDLINE (Ovid), Embase (Elsevier), CINAHL (EBSCOhost), EBM Reviews (Ovid), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment. We searched broadly for pressure ulcer treatments with a date range of 1985-2011. Gray literature was identified by soliciting stakeholders, TEP recommendations, and searching relevant Web sites, including clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, and the WHO International Clinical Trials Registry Platform), regulatory documents (Drugs@FDA and Devices@FDA), conference proceedings and dissertations (Conference Papers Index [ProQuest CSA]), Scopus (Elsevier), Dissertations & Theses (ProQuest UMI), and individual product Web sites. An additional focused search strategy on hyperbaric oxygen for the treatment of pressure ulcers was conducted at the recommendation of our TEP due to the paucity of evidence on this subject obtained from the original search. We conducted a second search in MEDLINE (Ovid) for references of hyperbaric oxygen in conjunction with pressure ulcer treatment (see Appendix A).

Scientific information packets (SIPs) were requested from identified drug and device manufacturers, and a notice inviting submission of relevant scientific information was published in the Federal Register. All interested parties had the opportunity to submit data for this review using the AHRQ Effective Health Care publicly accessible online SIP portal

(http://effectivehealthcare.ahrq.gov/index.cfm/submit-scientific-information-packets/). Reviewers evaluated received SIPs for data relevant to our review.

Additional studies were identified by reviewing the reference lists of published clinical trials, systematic reviews, and review articles.

The literature searches will be updated during the peer review process, at which time the additional studies will be evaluated and those meeting the inclusion criteria will be synthesized for the review.

Inclusion and Exclusion Criteria

The criteria for inclusion and exclusion of studies were based on the key questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. We used the following inclusion criteria (See Appendix B for details):

Populations: Studies were limited to adults aged 18 years and older being treated for existing decubitus ulcers. Subgroups included sex, race/ethnicity, socioeconomic status, and diverse specific medical comorbidities (e.g., diabetes, end-stage renal disease, dementia), and patients with specific known risk factors for pressure ulcers (e.g., nutritional status, incontinence, peripheral vascular disease, mobility limitations, functional ability). Studies conducted in populations including children, adolescents, and patients with non pressure-related ulcers, including but not limited to venous ulcers and diabetic foot ulcers, were excluded because treatment considerations for these patients may differ significantly from those for pressure ulcers.

Interventions: For efficacy and effectiveness assessments, all studies of interventions for treatment of pressure ulcers meeting the requirements of the PICOTS and Key Questions were included. Treatments for pressure ulcers included, but were not limited to: support surfaces, nutritional supplementation, wound debridement and cleansing, wound dressings, biologic agents, and surgical repair. Adjunctive therapies included ultrasound, electrical stimulation, vacuum-assisted closure, and hyperbaric oxygen therapy.

Comparators: Included usual care, placebo, no treatment, or different treatment interventions. Studies with no comparator were included for the assessment of harms only.

Outcomes: Studies reporting clinical outcomes of complete wound healing, wound surface area reduction, pain, prevention of sepsis, prevention of osteomyelitis, recurrence rate and harms of treatment care settings, (including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training) were included. Studies of non-healing ulcers were not included. We excluded studies that only evaluated non-clinical outcomes, cost, comfort, or nursing time required to administer the intervention.

Timing: No minimum followup time was required. Studies published prior to 1985 were not included.

Setting: We included studies conducted in patient-care settings such as home, nursing facility, or hospitals. We excluded studies in hospice settings if complete wound healing was not an outcome measured.

Study design: We included randomized trials, cohort studies, and case-control studies pertinent to all key questions. If such studies were not available, we included cross-sectional studies and intervention series studies. We included multicenter surgical intervention series with a population of 100 patients or more. Systematic reviews were used as background information

or to ensure completeness of the literature search. Case studies of only one patient were not included.

An initial scan of the literature revealed that studies of surgical interventions included primarily small series of specific surgical techniques performed at single centers. Because surgical outcomes are heavily influenced by individual surgeons, local practice patterns, and other contextual factors, our TEP raised concern that data from these small single-site studies ($n< 50$) would have limited generalizability, and that they would not provide a sound basis for making indirect comparisons across studies. We therefore excluded small single-site studies reporting the results of specific surgical techniques for pressure ulcer management. We originally planned to include only multicenter studies, but due to a paucity of evidence, based on input from our TEP, we expanded our inclusion criteria to include single-center studies reporting a large series($n\geq 50$) of patients undergoing surgery for pressure ulcer, as these were felt to have greater generalizability. We included studies that provide direct, head-to-head comparisons of different surgical techniques.

According to guidance from the European Pressure Ulcer Advisory Panel (EPUAP), and suggestions of literature from our Key Informants, the most relevant evidence about modalities and procedures for treating pressure ulcers used in clinical practice today comes from investigations conducted within the past 25 years therefore we limited the search to 1985 to present. Guidance from our TEP indicated that current literature (1985 to present) not only captures historically significant treatments and evidence, but also provides the most current information and treatments currently used in clinical practice. Non-English language studies were included in the abstract triage and translated for full-text review as feasible. Gray literature including unpublished data, abstracts, dissertations, and individual product packets from manufacturers were solicited, to be included if they added meaningful data or other information beyond what is found in the published literature.

Study Selection

To enhance consistency and reduce bias in our study selection process each reviewer evaluated the same set of 200 citations for inclusion and kappa values were calculated to estimate inter-reviewer reliability. After discussing and reconciling disagreements between reviewers, the same four team members reviewed an additional 100 citations. This process was continued until a kappa value of >0.50 for each pair of reviewers was reached. For the remaining references each reviewer evaluated each title and abstract for inclusion and exclusion, using the pre-established inclusion/exclusion criteria to determine eligibility for inclusion in the evidence synthesis. To ensure accuracy, a senior investigator/clinician conducted secondary reviews of all excluded abstracts. All citations deemed appropriate for inclusion by one or both of the reviewers were retrieved for full-text review.

Each full-text article was independently reviewed by two team members. When the two team members did not agree on inclusion or exclusion of an article, they met to discuss and reach consensus, and then the article was either included or excluded accordingly. In cases of when consensus was not reached by the two initial reviewers, a senior investigator reviewed the article and adjudicated the decision on inclusion or exclusion. Appendix E contains a record of excluded studies with reasons for exclusion.

Data Extraction

Data from included studies were extracted into evidence tables and entered into electronic databases using Microsoft Excel® and DistillerSR systematic review software (Appendix A). The data extracted into evidence tables included: study design; year, setting, duration, study inclusion, and exclusion criteria; population and clinical characteristics (including sex, age, ethnicity, comorbidities, functional ability, and ulcer stage); intervention characteristics; results for each outcome of interest; and withdrawals due to adverse events. Outcomes of interest for effectiveness were: resolution of ulcer determined by complete wound healing, healing time, reduction in wound surface area, and reduction in pain, prevention of serious complications of infection such as sepsis or osteomyelitis, and ulcer recurrence rates. Outcomes of interest for harms were: pain, dermatologic reactions, bleeding, and complications including but not limited to infection and need for surgical intervention. Data on settings included patient-care settings such long term care or nursing facilities, hospital, and community. If available, we also extracted the number of patients randomized relative to the number of patients enrolled, how similar those patients were to the target population, and the funding source. We recorded intention-to-treat results when available. All summary measure data was collected as available and presented in the individual studies, including but not limited to, percentage of complete wound healing, relative risk and risk ratios, confidence intervals, and significance values. A second team member verified all study data extraction for accuracy and completeness.

One of the challenges in extracting data from PU studies is that various systems have been used to assess the severity of pressure ulcers. Most use a four-stage categorization with higher numbers indicating higher severity.[7] In 2007 the United States National Pressure Ulcer Advisory Panel (NPUAP) redefined their four-stage classification system that defines the pressure ulcer based on depth and tissue involvement. (Figure X) Stage I is defined as superficial erythema, stage II as partial thickness ulceration, stage III as full thickness ulceration, and stage IV as full thickness with involvement of muscle and bone. A corresponding four stage classification system was similarly adopted by the European panel and this has now taken precedence for categorizing pressure ulcers. Given that the stages are based on depth and tissue involvement, when an ulcer has overlying purulent material or eschar prohibiting the ability to determine the depth or extent of tissue involvement, the ulcer is classified as unstageable, or stage X. A description of the most commonly used systems to classify pressure ulcers prior to adapting the NPUAP system is reviewed in Appendix C and aligned with the current corresponding NPUAP stage.

In order to allow comparability across studies, we extracted the stage or grade reported, but used the corresponding NPUAP stage in summary tables and text when possible.

Quality Assessment of Individual Studies

In this report, risk of bias is denoted as quality, with the following summary categories:

- Good quality is defined as a low risk of bias.
- Fair quality is defined as a moderate risk of bias.
- Poor quality is defined as a high risk of bias.

We used predefined criteria to assess the quality of controlled trials and observational studies at the individual study level (Appendix F). We also adapted criteria from methods proposed by Downs and Black[8, 9] (observational studies) and methods developed by the U.S. Preventive Services Task Force.[10]

We rated the quality of each controlled trial based on the methods described in the published reports about randomization and allocation concealment; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intention-to-treat analysis; and ascertainment of outcomes.[9] Individual studies were rated as "good," "fair," or "poor" (see Appendix F). Studies rated "good" have the least risk of bias, and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" do not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as they are to reflect the true differences between the interventions that were compared. We did not exclude studies rated poor quality *a priori*, but poor-quality studies were considered to be less valid than higher-quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Data Synthesis

Due to the heterogeneity of outcomes reported, variation in the comparators to which interventions were compared, and the limited number and quality of studies for specific treatment comparisons, quantitative analysis was not appropriate for most bodies of literature included in this review. For most comparisons, we therefore synthesized data qualitatively.

We evaluated the appropriateness of meta-analysis based on clinical and methodological diversity of studies and statistical heterogeneity. We conducted meta-analysis in selected instances for comparisons examining the outcome of complete wound healing, where the number, quality, and homogeneity of studies permitted. We chose to limit meta-analysis to the outcome of complete wound healing because of: a) variability in the measurement of other outcomes including wound size reduction, and b) indication from our TEP that complete wound

healing was the principal health outcome of interest. When meta-analysis was conducted, we used relative risk as the effect measure. We assessed the presence of statistical heterogeneity among the studies using standard χ^2 tests, and the magnitude of heterogeneity using the I^2 statistic.[11] We used random effects models to account for variation among studies.[12] and fixed effects Mantel-Haenszel models when variation among studies was estimated to be zero. Sensitivity analysis was conducted to assess the impact of quality on combined estimates and meta-regression was conducted to assess the association of effect measure with study duration. However, exploration of heterogeneity was typically limited by the small number of studies for each treatment category. All quantitative analyses were performed using STATA 11.0® (StataCorp, College Station, Texas, 2011)

Strength of the Body of Evidence

Within each key question, we graded the strength of evidence for effectiveness by intervention/comparator pair, and for harms by intervention, using an approach adapted from the AHRQ Methods Guide for Comparative Effectiveness Reviews. Our approach considers four major categories to rate the strength of evidence:

- Quality of studies (good, fair, poor)
- Consistency (low, moderate, or high)
- Directness (direct or indirect)
- Precision (low, moderate, or high).

As with our ratings of individual study quality, we used the terms "quality" in lieu of "risk of bias" in rating the overall strength of evidence of a given finding, with good quality defined as low risk of bias. Fair quality defined as moderate risk of bias, and poor quality defined as a high risk of bias. Our ratings for consistency and precision were trichotomous (low, moderate, high) rather than dichotomous (consistent vs. inconsistent, precise vs. imprecise), to allow for a more graded assessment of those domains. For the domain of "directness," we rated evidence from head-to-head comparisons as direct. We did not incorporate the distinction between ultimate outcomes (e.g., complete wound healing) and intermediate/surrogate outcomes (e.g., wound size reduction) into our ratings for directness. We did, however, give greater weight to studies demonstrating an effect on complete wound healing, as opposed to wound size reduction, based on input from our TEP that complete wound healing represents the most clinically important outcome of interest in pressure ulcer treatment.

We did not incorporate the domain of "dose-response association" into our strength of evidence ratings because few if any studies in our review included varying levels of exposure. We also did not include the domain of "plausible confounding that would decrease observed effect," because this domain is relevant primarily for observational studies, and nearly all of our findings were based on the results of clinical trials. The domain of "strength of association" is likewise relevant primarily for observational studies, where unmeasured confounders might reduce the strength of an observed association.

We were not able to assess publication bias using a quantitative approach for most treatments, since in most cases we were not able to perform a formal pooled analysis due to the heterogeneity of interventions, comparators, or outcomes, or due to the poor quality of studies. We did attempt to evaluate the possibility of publication bias by qualitatively examining the directionality of study findings by sample size for a given intervention, and by looking for unpublished studies through our gray literature search.

The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient— Evidence either is unavailable or does not permit a conclusion.

Applicability

Applicability is an indicator of the extent to which research included in a review might be useful for informing clinical and/or policy decisions. Applicability depends on the particular question and the needs of the user of the review. Because it depends on context, there is no generally accepted universal rating system for applicability. We described features of the included studies that are relevant to applicability in terms of the elements of PICOTS (populations, interventions, comparators, outcomes, timing and settings). These elements are the features embedded in the key questions that inform clinical decision making and the degree to which the evidence is likely to pertain to the subpopulations. For example, it is important to determine whether techniques described in studies are representative of current practice. We based our approach on the guidance described by Atkins, et al.[9, 13]

Peer Review

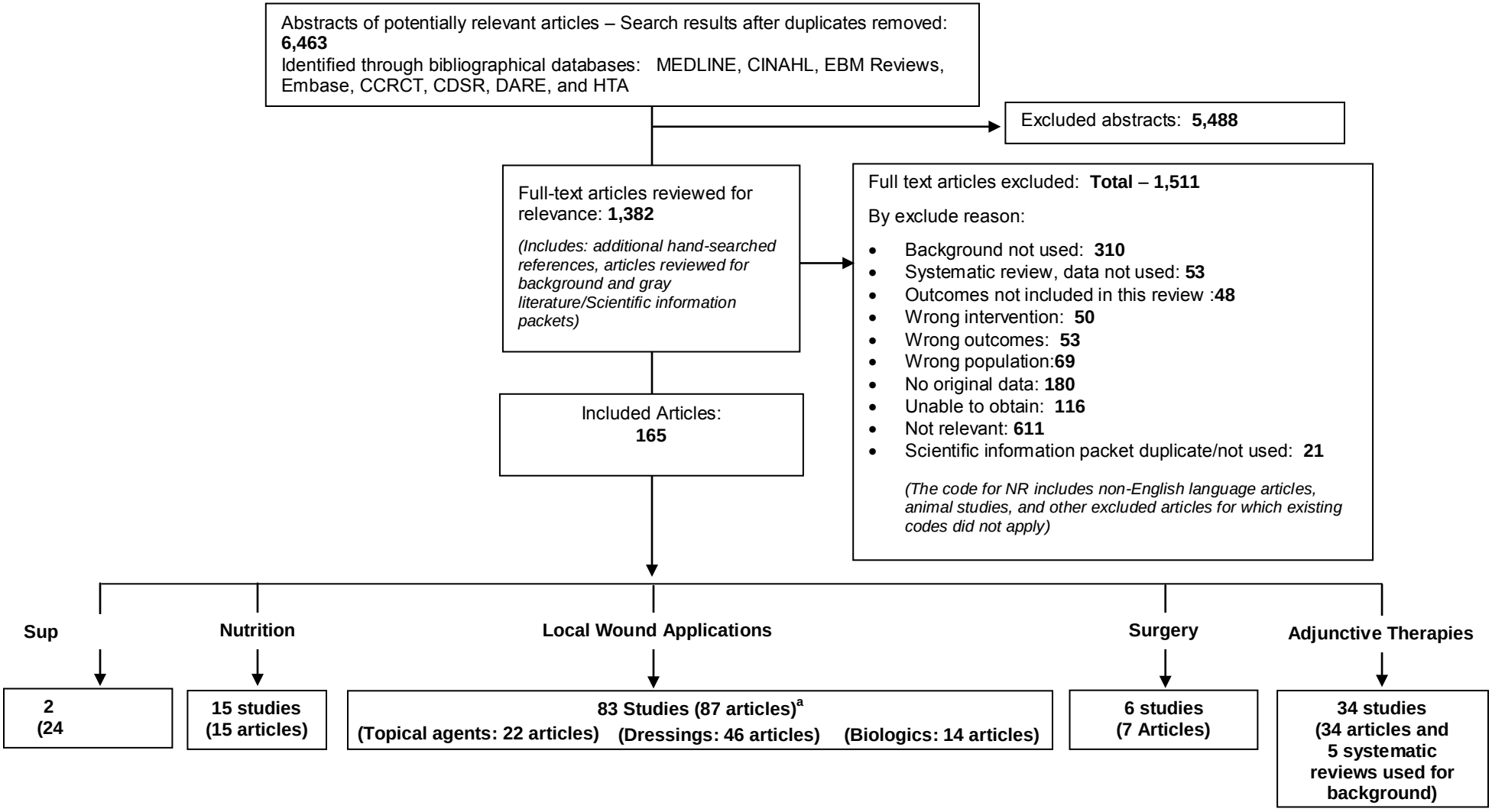
Experts in prevention and management of pressure ulcers, geriatric medicine, wound care research, and epidemiology, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ task order officer and a designated EPC associate editor will also provide comments and editorial review. To obtain public comment, the draft report will be posted on the AHRQ Web site for 4 weeks. After addressing the public and peer review comments, a disposition of comments report detailing the changes will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

Overview

The results of the search and study selection are summarized in the study flow diagram (Figure 4). Searches of databases, reviewing reference lists of published studies, and review of gray literature in resulted in 6,463 potentially relevant articles. After dual review of abstracts and titles 1,382 studies were selected for full text review, and 165 full text articles were included in this review. See Appendix B for complete inclusion exclusion criteria and Appendix G for strength of evidence assessment.

Figure 4. Study flow diagram: Comparative effectiveness of treatment for pressure ulcers



Abbreviations: MEDLINE: Medical Literature Analysis and Retrieval System Online; CINAHL: Cumulative Index to Nursing and Allied Health Literature; EBM Reviews: Evidence-Based Medicine Reviews; Embase: Excerpta Medica Database; CCRCT: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effectiveness; HTA: Health Technology Assessment.

Overall Effectiveness of Pressure Ulcer Treatment

Pressure ulcer treatment encompasses numerous intervention strategies: alleviating the conditions contributing to ulcer development (support surfaces, repositioning, nutritional support); protecting the wound from contamination, creating a clean wound environment, and promoting tissue healing (local wound applications, debridement, wound cleansing, various adjunctive therapies); and surgically repairing the wound. We evaluated evidence addressing the comparative effectiveness and harms in treatment categories where significant uncertainty exists about the best therapeutic options. Results for each key question are presented here, within these specific treatment categories: support surfaces, nutrition, local wound applications (including wound dressings, topical therapies and biological agents), surgical interventions, and adjunctive therapies. The overall findings of this review and a summary of the strength of the evidence for the key findings are presented in Table 16.

Results of Pressure Ulcer Treatment by Treatment Strategy

Effectiveness of Support Surfaces

Many factors contribute to both the development of pressure ulcers (PUs) and the likelihood that PUs will heal once they develop. However, pressure, friction, or shear that limits blood flow and/or damage to skin and underlying tissues are the most direct contributors to the development of PUs. Treatments that redistribute pressure are used to promote healing and prevent future damage to the skin in the area of the ulcer.

Pressure redistribution can be accomplished by a variety of types of support surfaces. A support surface is defined as: "A specialized device for pressure redistribution designed for management of tissue loads, micro-climate, and/or other therapeutic functions (i.e., any mattress, integrated bed system, mattress replacement, overlay, or seat cushion, or seat cushion overlay)."[14] While support surfaces are frequently used to prevent PUs for people at risk, they are also used and have been studied as a component of treatment of existing ulcers.

Description of Studies

We identified 22 studies of the use of various support surfaces in the treatment of pressure ulcers that met our inclusion criteria (see Appendix D). These studies were reported in 24 articles published between 1987 and 2010. Two studies were reported in more than one article.[15-18] Details extracted from each study are included in the evidence tables (see Appendix H). Of these, four were rated as good quality, 10 as fair, and eight as poor. The assessments of the criteria used for each study in order to arrive at the rating are provided in Appendix F.

Of the 22 studies identified, 20 were randomized trials. The other two included one trial in which the method of assignment was not clearly stated[19] and one large retrospective cohort study.[20] Twelve of these studies were conducted in the United States,[20-31] seven in the United Kingdom,[15-18, 32-36] and one each in Holland,[37] Japan,[19] and Belgium.[38]

The *populations* in the studies were predominately older hospital patients and long-term care residents. Mean ages were in the late 60s to 80s, with the exception of one study of people with spinal cord injuries living in the community. In this study the mean ages for the treatment and control groups were 42 and 45.[26] All subjects had at least one PU. The stage varied, with most studies including people with a range of ulcer severities (see details in Summary Table 16),

though some studies were limited to patients with ulcers of a particular stage (e.g., Stage II[16, 33] or Stage I[35]).

The *interventions and comparators* in studies of support surfaces as part of PU treatment include several different types of surfaces and brands. Support surfaces vary in terms of form factor (e.g., mattress, mattress overlays, seat cushions and seat overlays), materials, action, and method of pressure redistribution or environment control. Currently there is no universally accepted classification of support surfaces. Studies, reviews, and guidelines have classified support surfaces based on reimbursement policies;[20, 39] the primary action such as constant low pressure (CLP), low-air-loss (LAL), alternating pressure (AP), or air fluidized (AF); whether they require power or not for operation;[7]or as "low-tech" compared with "high tech.[40, 41]There is significant overlap with non powered, often equivalent to CLP, and "low tech," while powered is often AP or AF and considered "high tech." However, this categorization does not allow for the possibility of a high tech material or design that does not require power. Some studies compared a new design with AP as "standard care." For this reason we organized our presentation of the studies into four groups (AF, AP, LAL and "other") based on the surface that is considered to be the experimental group. The "other" category corresponds to the low tech or non powered category used in the prior reviews.

The *outcomes* measured and reported in the identified studies reflect the goals of treatment but were restrained by the *timing* of possible followup measurement, which ranged from 5 days[35] to 36 weeks.[27] The ultimate goal and therefore *outcome* of PU treatment is complete healing of the wound. Seven of the identified studies reported how many patients in the study had PUs that healed[22, 31-33, 35-37] and two also reported the time to complete healing[28, 33] while one reported time to 30 percent healed.[26] Most PUs, particularly larger ulcers and those that involve many layers of tissue, often require months to heal,[14] and some never heal completely in the patient's lifetime. Given these constraints, the majority of studies (15 of 22) included in this review[17-26, 29, 30, 32, 33, 36, 38] reported changes in the surface area or volume of either an index ulcer (usually the worst) or all PUs over either a set period of time or until the patient was discharged or died. An additional outcome reported in seven studies was simply "improvement." This variation on healing or change is size was defined as change in the stage of the ulcer or blinded assessment by experts.[15, 16, 19, 24, 25, 27, 34, 38] Five studies also reported pain or patient comfort as an outcome[17, 18, 21, 24, 29, 32] and two included hospital admissions and emergency department visits[20, 27] as an outcome compared across patients treated on different surfaces.

The *setting* for these studies included hospitals, long-term care facilities (e.g., nursing homes, post acute care facilities, and home health care agencies), and the community. Ten studies were conducted in acute care hospitals[15, 16, 21, 24, 25, 29, 30, 33-35, 38] and nine in long-term care facilities.[19, 20, 22, 23, 27, 28, 31, 32, 37] One study was of people living in the community[26] and two included both hospital patients and nursing home residents.[17, 18, 36]

Key Points

- Five studies that involved comparing air-fluidized beds with other surfaces all reported better healing in terms of reduction in PU size or stage on air-fluidized beds (strength of evidence: moderate).
- There was no evidence of differences in healing or reduction in ulcer size across different brands and types of alternating pressure beds (four studies, strength of evidence: moderate).

- The evidence about the effectiveness of alternating pressure beds compared with other types of beds was inconclusive with studies producing mixed results (three studies, strength of evidence: insufficient).
- Two studies of alternating pressure chair cushions were conducted in two very different populations (younger people with spinal cord injury and older hospital patients or nursing home residents) and produced different results, making it difficult to draw a generalizable conclusion about AP chair cushions (strength of evidence: insufficient).
- There was no evidence of differences in outcomes with LAL beds compared with foam surfaces (three of four studies), or with LAL beds compared with LAL overlays (strength of evidence: moderate).
- Four studies of surfaces presented as innovative and/or more cost effective involved different experimental surfaces and therefore did not permit generalizations (strength of evidence: insufficient).
- There was insufficient evidence to draw conclusions about the impact of patient or setting characteristics on the effectiveness of different support surfaces in PU healing.

Detailed Analysis

The identified studies are grouped by the type of support surface that was considered the experimental surface in both the summary of evidence in Table 16 and the narrative below.

Evidence about the Comparative Effectiveness of Support Surfaces (Key Question 1)

Air-Fluidized (AF) Beds

AF beds are made of small beads and air is forced through the beads to create a fluidlike surface that redistributes pressure. The five studies of air-fluidized AF beds were all conducted in the United States and included one large, fair-quality cohort study and four randomized trials. One trial was rated as good quality, two as fair, and one as poor. The combined results of these studies provide moderate evidence that AF beds have a positive effect in that they are more effective than alternatives in promoting the healing of PUs (Table 1).

The one good-quality randomized trial compared 31 hospitalized patients on an AF bed with 34 patients on an alternating pressure (AP) bed with a foam overlay, which was conventional treatment at the location of the study.[24] Those on AF beds experienced a median decrease in the size of their PUs (-1.2 cm^2) that was significantly better than the median increase (+0.5 cm^2) in the size of PUs in patients on the AP beds. Blinded assessors rated 71 percent of patients on the AF beds as improved compared with 47 percent on the AP.[24] A fair-quality study of hospital patients[29] compared 20 people on AF beds with 20 on standard hospital beds and reported that the mean ulcer area declined on the AF beds and increased for those on standard beds and that pain declined for all patients and did not differ by bed type. A third study (poor quality) of hospital patients compared 15 patients on AF beds with 20 patients that used several alternatives that were standard care and found wound surface area reductions were higher in the patients treated on the air-fluidized beds.[25]

The other two studies of AF beds were in long-term care settings and similarly report favorable results. One followed 97 home care patients randomized to either an AF bed (n=47) or conventional treatment (n=50). The authors reported that more stage III and IV ulcers healed to stage II on the AF beds (29 of 47, data for control group not provided) and a higher proportion

were rated as improved by blinded nurse raters.[27] A large retrospective cohort study (n=664) of residents with at least one PU in their medical record examined healing rates across AF beds, low-tech surfaces and high-tech surfaces other than AF beds. Comparisons were made for healing rates for the largest ulcer for each person as well as the change in each ulcer (multiples allowed per resident) during seven to 10 day episodes. Stage III and IV ulcers healed more quickly for patients on the AF beds (3.1 cm^2 per week) compared with other high- (0.7) and low-tech surfaces (0.6). Residents on AF beds and residents on lower tech surfaces (who overall were less severely ill) had fewer hospitalizations and emergency room visits than did residents who used the other higher tech beds.[20]

Table 1. Support surfaces: Air-fluidized beds

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage NPUAP (as reported)	Age Sex Population	Followup	Surfaces Compared (A=Experimental; B ,C=Comparison)	Outcome Measures and Treatment Effect	Benefit: Wound Healing
Allman 1987[24] Quality: Good n=72/65 Setting: Hospital	Stage I, II, III, IV and unstageable (Superficial= Shea scale stage 1 or 2; Deep= Shea scale stage 3, 4, 5 and eschar)	Age: 66.6 years Female: 73.8% (48 of 65) Population: General	13 days(4 to 77 days)	A. AF bed (Clinitron Therapy) n=31 B. AP-air covered with foam (Lapidus Air Float) n=34.	Wound Healing : 20/31 vs 15/34 P=.10 Median reduction in size: AF -1.2 cm^2 vs. +0.5 median increase in AP with foam. Regression results: AF 5.6 fold odds of improvement	~
Jackson 1988[25] Quality: Poor n=35 Setting: Hospital	Stage II, III, IV (Stage III, IV or V PU using Montefiore Medical Center System)	Age: 77.0 years) Female: 63.3% (21 of 33) Population: General	Until dis-charge	A. AF mattress; n=15 B. Several other different surfaces (not specified) n=20.	PU area reductions greater on AF than in control group (60% of patient decrease vs. 45%; statistical test not reported). Changes in stage were not significantly different.	+
Munro 1989[29] Quality: Fair n=40 Setting: VA Hospital	Stage II, III (Stage II, III using Phipps 1984)[42]	Age: 67.2 years Female: 0 (all male veterans) Population: General	15 days	A. AF bed (Clinitron Therapy) n=20 B. Standard hospital bed n=20	Mean ulcer area declined for patients on the AF bed and increased for those on the standard bed and this different was significant (p=0.05) Pain declined in both groups over time and there was no significant difference.	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage NPUAP (as reported)	Age Sex Population	Followup	Surfaces Compared (A=Experimental; B ,C=Comparison)	Outcome Measures and Treatment Effect	Benefit: Wound Healing
Strauss 1991[27] Quality: Fair n=97/69 Setting: Home Care	Stage III, IV (Stage 3 or 4 Shea classification)	Age: 64 years Female: 49.1% (55 of 112) Population: General	36 weeks	A. AF bed (Clinitron Therapy) n=58 randomized; 47 complete data. B. Conventional or standard therapy n=54 randomized, 50 complete data.	29/47 healed to Stage 2 and were removed from AF bed. Number healed not reported for control. Higher proportion of AF assessed as improved by 2 blinded nurse reviewers. AF had fewer hospital days and used fewer inpatient resources.	+
Ochs 2005[20] n=664 Quality: Fair Setting: Nursing home/ long-term care	Stage I, II, III, IV and Eschar (All stages, cites AHCPR Practice Guideline, 1984)	Age: 77.5 years Female: 69.2% (418 of 664) Population: General	3 months	A. AF beds n=82. B. Low tech surfaces n=463. C. High tech except AF n=119.	Mean Healing for residents with Grade III and IV ulcers with baseline size 20 cm^2 to 75 cm^2 (cm^2/week) Resident level/episode-ulcer level AF: 5.2/3.1 Other higher tech:1.8/ 0.7 Lower tech:1.5/ 0.6 ANOVA on both levels were significant.	+

Note: AF, air-fluidized; AP, alternating pressure; NPUAP, National Pressure Ulcer Advisory Panel; PU, pressure ulcer.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Alternating Pressure Beds and Chair Cushions

Alternating pressure mattresses, overlays, and cushions have cells or sections that inflate and deflate to change the distribution of pressure. The sizes of the cells, patterns of inflation and deflation, and the length of the cycles can vary across brands. Nine studies—six conducted in the United Kingdom and one each in Belgium, Japan, and the United States—evaluated AP mattresses or chair cushions (Table 2).

Different Brands or Form Factors of Alternating Pressure Beds

Researchers found no significant differences in healing in the three studies that compared different AP beds, all involving a version of the Nimbus brand bed. One study that compared AP beds with AP overlays also found no significant difference in the number of ulcers that healed or the number of days they took to heal (moderate strength of evidence).

A fair-quality study of residents admitted to a geriatric hospital in Scotland found that in 4 weeks 10 of 16 patients on the Nimbus 1 AP bed healed compared with five of 14 who used the Pegasus brand AP bed, but this difference was not significant and the study was stopped after 2 years due to difficulties with recruitment and changes in the beds. Researchers comparing a later version of the same AP mattress (Nimbus 3) with other brands of AP mattresses in a good quality study found no significant difference in change in size of the PUs in 12 hospital patients and 20 nursing home residents though there were some differences in comfort, with the Nimbus 3 rated as more comfortable.[17, 18] The third study (fair quality) found a trend toward improvement in heel ulcers on the Nimbus 3 beds compared with another brand (Pegasus Cairwave), but there was no significant difference in healing for sacral ulcers.[15, 16] The protocol for a good quality study that compared an AP mattress to an AP overlay reported no statistically significant differences in the number of ulcers healed or the median time to healing.[33]

Alternating Pressure Beds compared with Other Surfaces

Three studies (two fair quality and one poor) evaluated alternating pressure surfaces by comparing them with other surfaces for patients. The studies included patients with PUs at all stages[19, 34, 38] and the findings were inconsistent (strength of evidence: low).

Two studies followed elderly hospital patients until discharge.[34, 38] One found no significant difference in ulcer progress for 83 patients treated on the AP mattress compared with 75 patients treated on a fluid overlay.[34] The most recently identified study of hospitalized patients compared patients on ventilators on AP beds with patients on air overlays and documented significant improvement (reduction in wound surface area) on the AP mattress, however the sample size was small (n=16).[38] A poor-quality trial involving long-term care hospital patients in Japan found no significant difference in change in PU surface area in patients on a specific type of AP bed (lateral rolling bed which moves residents from left side to back to right side on a timed cycle) compared with a traditional hospital bed; however, the mean stage of the PUs for patients on the rolling bed declined while the mean stage increased on the standard hospital bed.[19]

Alternating Pressure Chair Cushions

Alternating pressure is also used in chair cushions. Two studies compared AP cushions used in wheelchairs or day chairs with other types of cushions.[26, 36] The one study of AP surfaces, cushions or beds, conducted in the United States, randomized 44 wheelchair users with spinal cord injuries living in the community who had stage II or III PUs to either an AP cushion or a standard foam cushion for their wheelchair for 30 days. People using the AP cushion experienced significantly better rates of healing measured as reduction in wound area, days to 30 percent wound closure, and probability of wound closure within 30 days.[26]

The second study of AP cushions included 25 hospital or nursing residents who used an AP cushion or a dry floatation cushion in their wheelchair or day chair. PUs healed for three of 14 patients on AP cushions and five of 11 on the dry floatation cushions; however, this difference was not significant.[36]

Table 2. Support surfaces: Alternating pressure beds and chair cushions

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage NPUAP (as reported)	Age Sex Population	Followup	Surfaces Compared (A=Experimental; B=Comparison)	Outcome Measures and Treatment Effect	Benefit: Wound Healing
Alternating Pressure (AP) Beds: Different Brands or Forms						
Devine 1995[32] Quality: Fair n=41/30 Nursing home/ long-term care	Stage II or higher (Grade 2 or higher, Torrance cited as grading system)	Age: 82.5 years Female: 58.5% (24 of 41) Population: General	4 weeks	A. AP bed (Nimbus 1 n=22). B. AP bed (Pegasus Airwave) n=19.	No significant difference Number healed Nimbus 1: 10 of 16; Pegasus: 5 of 14 RR=1.75, P=non significant Reduction in size: Median per day Nimbus 1: 0.089 cm^2; Pegasus: 0.107	~
Evans and Land 2000[17, 18] Quality: Good n=32 Setting: Hospital and nursing home	Stage II, III, IV (Grade 2,3, 4 cited in Care, 1985)	Age: 81.1 years Female: 78.1% (25 of 32) Population: General	Until healing, discharge, or death.	A.. AP bed (Nimbus 3) n=17 B. AP bed (other brands) n=15	Change in size (Median absolute reduction per day, cm^2). Hospital: Nimbus 3: 0.12; Others 0.08 Nursing Home: Nimbus 3: 0.11; Others: 0.05 Relative reduction (%) also reported. None significantly different.	~
Russell 2000[15, 16] Quality: Fair n=141/112 Setting: Hospital	Stage I, II (Grade 2a = persistent erythema intact epidermis or 2b = persistent erythema epidermis loss. Also included Grade 3, 4,5 in description but not all analyses. Used Torrance Classification.)	Age: 84.2 years Female: Not reported Population: General	Discharge or healed	A. AP bed (Nimbus 3) and Aura seat cushion n=70 B. AP bed (Pegasus Cairwave) and ProActive seat cushion n=71	No significant difference in improvement Nimbus 91% (65/71); Pegasus 93% (65/70).	~
Nixon 2006[33] Quality: Good n=113 Setting: Hospital	Stage II (Grade 2= partial thickness wound involving epidermis or dermis only)	Age: 75.2 years Female: 63.9% Population: General	30 days	A. AP bed n=59 B. AP bed overlay n=54	Complete healing AP bed: n=20; (33.9%), 20 days. AP overlay: n=19 (35.2%), 20 days RR=0.963 Not statistically significant	~

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage NPUAP (as reported)	Age Sex Population	Followup	Surfaces Compared (A=Experimental; B=Comparison)	Outcome Measures and Treatment Effect	Benefit: Wound Healing
AP Beds vs. Other Surfaces						
Russell 2003[34] Quality: Fair n=199/158 Setting: Hospital	Stage I or higher (Grade I or higher EPUAP)	Age: 80.1 years Female: 54.4% Population: General	Until discharge; Average days AP=22.17 RIK=20.05 days	A. AP bed (Nimbus 3) n=83 B. Fluid overlay (RIK) n=75	No significant difference in worst ulcer per patient progress (p=0.053) or overall ulcer progress including all ulcers (p=0.67)	~
Malbrain 2010[38] Quality: Fair n=16 Setting: Hospital	Stage I, II, III (Grade 1, 2, 3, EPUAP)	Age: 64.7 years Female: 50% Population: Intensive care unit	Until discharge. Mean 11 days.	A. AP bed (Nimbus 3) n=8; 5 with PU on admission B. Air overlay (ROHO) n=8; 4 with PU on admission	AP significantly better in change in surface area (-2.1 cm^2 vs. 25.8; p=0.05) and change in PU category (-1 vs. 3.4; p=0.01).	+
Izutsu 1998[19] Quality: Poor n=31 Setting: Nursing home (long-term care)	Stage I, II, III, IV (Grades I-IV, description provided)	Age: 78 years Female: 58.10% Population: General	3 months	A. Lateral rolling bed n=19 B. Standard hospital bed n=12	No significant difference in wound size. Change in mean grade, pre-post within groups Rolling: 2.8 to 2.0; p<0.01 Conventional: 3.0 to 3.2; p>0.5	~
AP Cushions						
Clark 1998[36] n=33/25 Quality: Fair Setting: Hospital and nursing home	Unclear (Grade 2 and above-cites J of Advanced Nuring-1992	Age: 82.7 years Female: 72% Population: General	Weekly until PU healed, or discharged or died	A. AP cushion (Pegasus) n=14 B. Dry floatation cushion (ROHO) n=11 For use in wheel chairs and day chairs	Healed: 3/14 on AP cushion, 5/11 on ROHO. Not significantly different.	~
Makhsous 2009[26] Quality: Fair n=44 Setting: Community	Unclear (Stage II or III PUs, staging system not cited)	Age: 43.45 years Female: 6.8% Population: Spinal cord Injury wheel chair users	30 days	A. AP, cyclic pressure relief system n=22 b. Regular wheel chair cushions n=22	Significantly greater reduction in wound area p=0.001), fewer days to 30% wound reduction, and higher probability of 30% wound closure by 30 days (p=0.007) with the alternating pressure cushion. 30% wound closure RR= 2.00	+

Note: AP, alternating pressure; EPUAP, European Pressure Ulcer Advisory Panel; NPUAP, National Pressure Ulcer Advisory Panel; PU, pressure ulcer.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Low-Air-Loss Beds

Four studies evaluated LAL mattresses[21-23, 31] that use power to provide a flow of air that helps regulate heat and humidity and also may adjust pressure. All four of these studies were conducted in the United States. Two trials studied hospitalized patients and two studied nursing home residents. Three of the studies compared the LAL bed with a foam overlay while one compared an LAL bed with an LAL overlay (Table 3).[30]

None of the four studies found a significant advantage of the LAL bed in their primary outcome. Two of the studies in long-term care compared LAL beds with foam overlays and reported mixed findings for residents with stage III or IV PUs. One study found no significant difference in complete wound healing but did report a significantly larger reduction in surface area on the LAL bed.[22] Similarly, the second study reported higher rates of wound healing and improvements in terms of surface area but no significant difference in complete healing.[31]

One study of LAL beds used with hospital patients compared the LAL mattress with foam overlays and found no significant difference in changes in wound surface area and no significant difference in comfort.[21] The study that compared an LAL bed with an LAL overlay for hospital patients also reported that there was no significant difference in changes in PU surface area.[30]

Table 3. Support surfaces: Low-air-loss beds

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage NPUAP (as reported)	Age Sex Population	Followup	Surfaces Compared (A=Experimental; B=Comparison)	Outcome Measures and Treatment Effect	Benefit: Wound Healing
Day 1993[21] Quality: Poor n=118/83 Setting: Hospital	Stage II, III IV with limited activity (NPUAP used)	Age: 75.9 years Female: 57.8%) Population: General	Until discharge	A: LAL bed (TheraPulse) n=44 B: Foam overlay (GeoMatt) n=39	No significant difference. Change in wound surface area controlling for initial size (p>0.05). No significant difference in comfort reported by 39 patients.	~
Ferrell 1993[22] Quality: Good n=84 Setting: Nursing home (long-term care)	Stage III, IV (PU Stage 2 or higher Shea scale)	Age: 84.5 years Female: 50% Population: General	Until healed, death or transfer. Median LAL: 33 days, Foam: 40 days	A. LAL bed (Kinair) n=43 B. Foam overlay n=41	No significant difference in complete healing (26/43, 60% of LAL; 19/41, 46% on foam). RR=1.3 LAL significantly larger decrease in wound surface area (9.0 vs. 2.5 mm^2 per day; p=0.0002).	~
Mulder 1994[31] Quality: Poor n=49 Setting: Nursing home (long-term care)	Stage III, IV (Stage III or IV International Association of Enterostomal Therapists)	Age: Not reported Sex: Not reported Population: General	Shorter of 12 weeks or ulcer completely healed	A. LAL bed (Therapulse) n=31 B. Foam overlay (GeoMatt) n=18	No significant difference in healing: 5 vs. 3 healed. RR=0.97 LAL more effective in healing ulcers than foam in terms of change in ulcer area adjusted for initial stage (p=0.042)	~
Caley 1994[30] Quality: Poor n=93/55 Setting: Hospital	PU Stage not reported	Age: 76 years Female: 60% Population: General	1 month or until discharge; mean time in study 23.9 days	A. LAL bed (Monarch) n=23 B. LAL overlay n=32	Wound surface area change: not significantly different. Median change cm^2 Overlay: 3.9 bed: 1.9; p=0.06	~

Note: LAL, low-air-loss; NPUAP, National Pressure Ulcer Advisory Panel; PU, pressure ulcer.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Other Surfaces

Four studies compared a surface that was a new design, to a surface that was the standard of care at the time or conducted a cost-effective analysis. These four studies involved 361 total subjects; two were conducted in the United States, one in Holland, and one in the United Kingdom. The experimental surfaces included a high-quality foam mattress, a profiling bed, an airbed with a foam overlay, and a total contact seat. Given these differences and the overall quality of the studies (one fair and three poor quality) the evidence could not be summarized across the studies. Each study is described below and in Table 4.

Three of the studies were in long-term care settings. The one fair quality study followed nursing home residents randomized to either foam or water mattresses for 4 weeks. In that time the number of residents who were completely healed was not significantly different on the two

surfaces (45 percent on foam and 48.3 percent on water).[37] A randomized trial compared the use of a seat with customized shape and air bladders, a LAL bed, and a foam bed overlay in the treatment of nursing home residents and found that ulcers healed most quickly in patients treated up to 4 hours a day in the seat as opposed to a LAL bed or bed with overlay.[28] The third study in long-term care treated the LAL bed as the standard of care and compared it with a less expensive air bed with foam overlay for 20 patients in a post acute care center. The researchers reported that the wound surface area closures per week were similar or better on the air and foam bed (9 percent air/foam vs. 5 percent LAL, no statistical test or variance reported).[23]

A larger study of the incidence of PUs in hospital patients randomized patients to either a profiling bed (electronically controlled and designed to keep patients from slipping down in bed) or a conventional bed. The recruited subjects included 14 patients with stage I PUs on admission; four of the four on the profiling bed healed by discharge while two of ten assigned to conventional beds healed (no statistical tests reported).[35]

Table 4. Support surfaces: Other surfaces

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Support Surfaces Compared	Outcome Measures and Treatment Effect	Benefit: Wound Healing
Groen 1999[37] Quality: Fair n=120/101 Setting: Nursing home (long-term care)	Stages II, III, IV (Grade III=superficial cutaneous or subcutaneous necrosis or Grade IV = deep subcutaneous necrosis Grading system not cited)	Age: 82.5 years Sex: Not reported Population: General	4 weeks	A. High-quality foam replacement mattress (TheraRest) n=49 B. Water mattress (Secutex) n=52	No significant difference percent completely healed. Foam: 45% (22/49) Water: 48.3 % (25/52) RR=0.93	~
Keogh 2001[35] n=100/70 Quality: Poor Setting: Hospital	Stage I (Grade 1 EPUAP Grade)	Age: not reported Sex: Not reported Population: General	5 to 10 days	A. Profiling bed n=35; 4 with PU B. Conventional bed n=35; 10 with PU	4 of 4 patients on profiling bed healed; 2 of 10 on the conventional bed.	++
Branom 2001[23] Quality: Poor n=20 Setting: Long-term care hospital/ post-acute center	Unclear PU (Stage III or IV, staging g system not cited)	Age: 74.2 years Sex: Not reported Population: Bedridden	8 weeks	A. Air bed with foam overlay (PressureGuard CFT) n=10 B. LAL bed n=10	Average rate of wound healing per week: LAL: 5% vs. air/foam 9% no test given, summary data only presented.	+
Rosenthal 2003[28] n=207 Quality: Poor Setting: Nursing home (long-term care)	Stage III, IV (Stage III or IV, cites AHCPR Practice Guideline, 1984)	Age: 70.4 (seat), 69.0 (LAL), 6.6 (overlay) years Sex: Not reported Population: General	6 months or until healed	1. Generic total contact seat with adjustable air bladders (Sandia Labs) 2. LAL bed (TheraPulse) 3. Bed overlay-foam (Geo-Matt) n by treatment not reported	Mean time to complete healing in months Seat: 3.33 LAL: 4.38 Overlay: 4.55 Seat more rapid healing; no significant difference between LAL and overlay	++

Note: EPUAP, European Pressure Ulcer Advisory Panel; LAL, low-air-loss; NPUAP, National Pressure Ulcer Advisory Panel; PU, pressure ulcer.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Evidence about the Comparative Effectiveness of Support Surfaces by Subgroup-analysis (Key Question 1a, 1b, and 1c

Most of the studies of support surfaces identified for this review did not include any subgroup analyses. Four studies presented some results by PU characteristics,[15, 16, 21, 22, 28] addressing Key Question 1a, however the presentation was often limited and not necessarily part of the original analysis plan.

While initial stage of the PU or size at enrollment were incorporated into results by reporting changes or by including these as variables in regressions or ANOVA analyses, four of the 23 studies asked questions or presented results that address whether the effect of the support surface varied across differences in PUs.

In a study of hospitalized patients that compared two brands of AP mattresses, results were compared for PUs staged as IIa compared with IIb. There was no significant difference in healing on the two beds, whether the results were combined or separated by ulcer stage.[15, 16]

Nursing home residents using an LAL bed and a foam overlay were divided by whether their PUs were superficial or deep; however the results were the same for the two categories with residents on the LAL beds experiencing a larger decrease in wound surface area.[22]

A comparison of LAL beds with foam in hospitals presented the initial and end size of ulcers separately for stage II and stage III/IV, but the differences in healing were not discussed by PU stage by the authors and no test of differences by stage was provided. The data presented suggested that the change was similar on the two types of beds for stage II PUs, but that there was greater improvement on the LAL bed for stage III/IV PUs.[21]

In the comparison of a generic total contact seat with a LAL bed and foam overlay, the results were divided by the location of PU. PUs on the trochanter and coccyx healed more quickly on the total contact seat, while there was no significant difference in the time to complete healing for PUs located on the ischial tuberosity.[28]

None of the identified studies examined the impact of support surfaces by other patient characteristics (Key Question 1b).

None of the studies in a single setting reported on any relationships between setting characteristics and PU outcomes. Three studies included both hospital patients and nursing home residents, but only one reported the results separately and then only in one of two articles reporting the results of the trial.[18] In this study comparing a specific brand of AP bed (Nimbus 3) with any other AP beds, the results were examined together and separately for the 12 hospital patients and the 20 nursing home residents and no significant differences were found in wound size when the results were examined by setting.

Support Surfaces: Harms (Key Question 2)

Few of the identified studies, seven of 22, explicitly addressed harms attributable to support surfaces and harms were rarely mentioned in the study descriptions, discussions, or results of the articles about support surfaces. In the seven where harms were mentioned, four reported no significant differences in harms across the different support surfaces.

Four of the seven studies that mentioned harms were from the subgroup of five studies of AF beds. One study reported that one patient on the AF bed had a severe episode of epistaxis requiring a transfusion that might have been caused by the drying action of the bed and four patients had trouble transferring in and out of the AF bed.[24] Another study reported no significant differences in bleeding, granulation, necrosis, or nursing time on the AF beds compared with a variety of surfaces.[25] In a study comparing AF beds with standard hospital beds, the author stated that they tested for dehydration, pulmonary congestion, confusion, and microsphere leakage; they found that none of the patients experienced these problems.[29] The study of AF bed use in home care reported safety issues including minor mechanical problems that were corrected within 24 hours (six leaks and seven beds overheated), several cases (number not reported) of dry skin, and one case of mild dehydration.[27]

One[31] of the three studies of LAL beds compared LAL beds with foam overlays and mentioned that no harms were identified, but did not specify what harms were considered. Pain was reported as a complicating factor in another study and was found not to differ across the support surfaces (foam and water beds) during the course of the trial.[37]

A large trial (n=1972; but n=113 in the treatment subgroup) of AP beds and AP overlays for both prevention and treatment reported nine mattress-related adverse events (four falls, three other slips, one suspected contact dermatitis, and one patient who caught his back on the bed rail) for the entire trial but did not report whether these occurred in the prevention or treatment arm.[33]

Evidence about the Harms Related to Support Surfaces by Subgroups According to PU Characteristics (Key Question 2a), Patient Characteristics (Key Question 2b), or Setting (Key Question 2c)

None of the identified studies examined harms by any subgroups.

Effectiveness of Nutrition

Enhanced nutritional support for patients at risk of developing pressure ulcers is widely recognized as an important aspect of ulcer prevention. The European Pressure Ulcer Advisory Panel (EPUAP) and the National Pressure Ulcer Advisory Panel (NPUAP) combined international guidelines make specific recommendations for providing high-protein, mixed nutritional supplementation to patients at risk for pressure ulcer development.[43] However, the role of enhanced nutrition in improving treatment outcomes for patients who have developed pressure ulcers is less clear; many studies have evaluated the efficacy of oral and enteral nutritional interventions typically used to prevent ulcers, but only a small number of studies have assessed these interventions for treatment of existing ulcers.

Overall, nutritional interventions for pressure ulcer treatment fall broadly into three categories. These include *mixed nutritional supplementation* which consists of providing enhanced calories and vitamins with or without protein supplementation, *protein or amino acid supplementation* using high protein or amino acids with or without additional caloric support or vitamin supplementation to enhance wound healing and *specific nutrient supplementation* with vitamins or minerals such as ascorbic acid (vitamin C) or zinc.

Description of Studies

Spanning the three general categories of nutritional intervention we identified 15 studies of the use of nutritional supplementation in the treatment of pressure ulcers that met our inclusion criteria, 5 addressing mixed nutritional supplementation, 8 addressing protein or amino acid supplementation, and 2 addressing specific nutrient supplementation.[44-55, 56A, 57-60] (See Appendix B for detailed inclusion/exclusion criteria). Three of these studies were rated as good quality,[45, 51, 54] five were fair,[48, 52, 55, 56A, 57] and seven were poor quality. All of the studies had sample sizes under 100 patients, except for one study of 160 patients.[44, 46-50, 53, 58] Study data and the quality assessment of each study are presented in evidence tables (see Appendix H, Evidence Table 3). Of the studies identified, nine were randomized trials[44-52] and six were observational studies.[53-58] The included studies were published between 1990 and 2011.

The *populations* in the studies were predominantly older patients, some with mobility impairment, and although not all studies reported prior nutritional status, only one study was conducted among patients without reported baseline malnutrition.[52] Patients ranged in age from 49 to 83 years old, all subjects had at least one pressure ulcer, and the majority of studies included patients with ulcers ranging in stage from II-IV. Two observational studies also included patients with stage I ulcers[49, 58] (see details in Table 16).

The *interventions and comparators* varied widely across studies but generally included different types of nutritional interventions falling in three categories.

- Mixed nutritional supplementation
- Protein or amino acid supplementation
- Specific nutrient supplementation
    - Ascorbic acid (vitamin C) or zinc.

The *comparators* were standard care or placebo or high doses of a supplement compared with a lower dose of the same supplement and were used in combination with standard nutritional support or alone. One study compared a high-protein and high-calorie diet with amino acid supplementation.[46]

The key *outcomes* measured were complete wound healing, healing time, and reduced wound surface area. The most commonly reported harms were gastrointestinal events and infection.

The *timing,* or duration of followup, for all but two of the studies ranged from 3 to 12 weeks. Only one study evaluated patients for 12 months[55] and another study followed patients for 1 week.[49]

The *setting* for the studies included hospitals or long-term care facilities, and one study was conducted among people living in the community.[55] The studies were conducted in Australia, Europe, Japan, and the United States.

Key Points

- The study quality was generally low across studies of mixed nutritional supplementation. Studies reported small benefits in the reduction of wound size and reduced healing time. No significant benefit in terms of complete wound healing was reported. (strength of evidence: low).
- For studies of protein or amino acid supplementation, healing and reduction in ulcer size were similar to slightly better among patients receiving high protein, amino acids, or amino acid precursors compared with standard care, placebo, or other forms of supplementation (strength of evidence: low).
- The evidence about the effectiveness and the results of either vitamin C or zinc supplementation to enhance wound healing was inconclusive. Only two studies evaluated specific nutrient supplementation without overall additional nutritional support. One was a trial of the effect of high and low doses of ascorbic acid (vitamin C) that found no significant difference in wound healing and the other was an observational study of zinc supplementation (strength of evidence: insufficient).
- Harms or adverse events were reported in about half of the studies (eight of 15), but they reported different harms, did not describe the harm, or did not specify if it was related to treatment (strength of evidence: insufficient).

Detailed Analysis

Our analysis is by key question and the three categories described above. Within these categories of treatment, mixed nutritional supplementation includes studies that described combinations of enhanced calories, protein, and nutrients. The treatments used in the studies of protein or amino acid supplementation consisted of using high protein supplementation or amino acid precursors to determine if the added availability of amino acids (often specifically arginine) promotes wound healing. The specific nutrient supplements used were ascorbic acid (vitamin C) or zinc without additional nutritional support. The studies are summarized by intervention category in Tables 5, 6, and 7, and in the following description of the results. We were unable to conduct meta-analyses of nutritional supplementation treatment comparisons due to the small number, poor quality, and heterogeneity of studies for most treatment comparisons.

Evidence about the Comparative Effectiveness of Nutritional Supplementation (Key Question 1)

Nutritional Supplementation compared with Standard Nutrition or Placebo

Mixed nutritional supplementation was compared with conventional care or placebo in three randomized trials,[45, 50, 52] only one of which was rated good quality,[45] and in two observational studies, rated fair and poor quality.[57, 58] The combined sample size included a total of 230 patients studied. The PU stages of the patients varied in the studies (see Table 5 below). While all these studies found improvement in healing, the studies had flaws and small sample sizes.

The one good-quality trial compared either oral or tube fed nutritional supplements containing protein, arginine, vitamin C, and zinc to a standard hospital diets and found a modest benefit of mixed nutritional supplementation compared with standard nutrition over a 12-week followup period.[45] Complete wound healing occurred in one of 13 of the patients in the treatment group (7.7 percent) and no complete wound healing was reported among 15 patients receiving standard nutrition. Overall, the patients treated with the enriched formula had a significantly higher mean reduction in PU area (57 percent vs. 33 percent at Week 8, $p<0.02$; ~ 45 percent at Week 12, $p<0.005$).[45] Secondary analyses attempted to determine if particular nutrients were associated with healing and found a significant effect only for the whole formula, not the components.

A fair-quality trial analyzed data from 43 non malnourished patients who used a similar nutritional supplementation to the trial described above. The investigators found significant reduction in pressure ulcer size, determined by change in ulcer surface area, at 8 weeks in the intervention group receiving oral nutritional supplementation compared with patients who received placebo. Complete wound healing did not differ with 27 percent of ulcers healing completely in the intervention group compared with 24 percent of patients who received placebo.[52]

A third poor-quality trial suggested a moderate benefit of wound healing among 50 patients receiving mixed nutritional supplementation with higher calories. Thirty-three percent of patients receiving intervention compared with 13 percent of patients receiving standard enteral nutrition reported complete wound healing.

The observational studies included a retrospective examination of calorie and protein intake of patients whose PUs did and did not improve and reported that those who improved had higher calorie and protein intakes.[58] A second observational study reported a mean reduction in wound surface area of 29 percent over time, but did not include a comparison group that did not receive the supplements.[57]

Table 5. Nutrition therapy: Mixed supplementation

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/ Followup	Interventions/ Comparators	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Cereda 2009[45] Quality: Good N=30/28 Setting: Long-term care facilities	Stage II, III, IV	Age: 82 Female: 60% Population: Elderly	12 weeks	Oral nutrition supplement OR Enteral nutrition supplement **vs.** Standard hospital diet	Wound surface area reduction: significantly higher mean reduction in PU area (57% vs. ~ 33% at Week 8, p<0.02; 72% vs. 45% at Week 12, p<0.005).	+
Frias Soriano 2004[57] Quality: Fair N=63/39 Setting: Hospitals	Stage III-IV	Age: 75 Female: 54% Population: General	3 weeks	1-3 packages/ day of oral supplement	Wound surface area, mean reduction: 29% Healing time: 0.34 cm^2/day. No comparison group	+
Ohura 2011[50] Quality: Poor N=50 Setting: Hospital	Stage III-IV	Age: 81 Female: 68% Population: tube-fed patients	12 weeks	Standardized care plus Racol® enteral nutrition, with added calories vs. Standardized care plus Racol® enteral nutrition	Complete wound healing: Intervention: 33% (7 of 21) vs. Control: 13% (4 of 29) statistical test not reported Wound surface area: size decrease more rapidly in the intervention group (p<0.001)	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/ Followup	Interventions/ Comparators	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
van Anholt 2010[52] Quality: Fair N=47/43 Setting: Health care centers, hospitals, long-term care facilities	Stage III – IV	Age 75 Female: 56% Population: General	8 weeks	High energy enriched oral nutritional supplement, vs. Placebo	Complete wound healing: 27% (6 of 22) vs. 24% (3 of 21) statistical test not reported. Faster reduction in PU size in intervention group (p=0.0006)	+
Yamamoto 2009[58] Quality: Poor N=40 Setting: Hospital	Stage I-II	Age 69 Female: Not reported Population: patients with chronic diseases	6 weeks	Retrospective assessment of total energy intake through normal feeding and nutritional supplementation (oral, enteral, parenteral), with usual wound care and low-air-loss or extra-soft mattress.	Patients that healed or improved had higher total energy intake and protein intake, along with increased serum albumin levels and stable hemoglobin levels.	+

Note: NPUAP, National Pressure Ulcer Advisory Panel.
++ Complete wound healing.
+ Some improvement.
~ No difference.

Protein or Amino Acid Supplementation compared with Standard Nutrition or Placebo

Protein or amino acid supplementation was compared with standard nutritional care, placebo, and an amino acid or an amino acid precursor in eight studies.[44, 46-49, 53-55] The generally poor quality of the studies related to the small sample size provided only low strength of evidence on which to base any conclusion. Protein supplementation appeared to have a positive impact on PU healing, but this varied based on the patient baseline status and the sample sizes and the magnitude of the effects were generally small.

Five of the studies were randomized trials[44, 46-49] and three were observational.[53-55] One observational study was rated good[54] and one trial and one observational study were rated fair quality,[48, 55] while all of the remaining studies were rated poor quality.[44, 46, 47, 49, 53] These eight studies included a total of 454 patients and the studies were conducted in patients with ulcers ranging from stage I to stage IV.

The one good-quality observational study compared oral or enteral nutrition supplementation containing 14 percent protein to treatment with oral or enteral nutrition supplement that included 24 percent protein. The higher protein group experienced significant decline in wound size from

baseline to followup while the 14 percent group did not. This finding was the same for all patients as well as for patients with stage IV ulcers.[54]

The one fair-quality trial was a multicenter intervention with 160 patients conducted over 12 weeks among malnourished elderly hospital patients with stage II, II, and IV heel ulcers.[48] The study randomly assigned patients to receive ornithine alpha-ketoglutarate (an amino acid salt precursor to the amino acids glutamine, arginine, and polyamines including proline) once a day or placebo for 6 weeks and followed patients after discharge. The outcomes were mean wound surface area reduction and rate of closure. In patients with smaller ulcers at baseline (≤ 8 cm^2) the patients receiving the supplement experienced higher reductions in wound area and wound closure rates than patients receiving the placebo. However in patients with larger PUs at baseline (>8 cm^2), there was no significant difference in closure rates or wound area reduction.

The one fair-quality observational study compared people living in the community with spinal cord injuries who consumed an arginine supplement every day until their PU healed to historical controls. Ulcers healed faster (mean 10.5 weeks vs. 21 weeks) in patients taking the supplements compared and this difference was statistically significant.

The findings of the four poor-quality trials and the one poor quality observational study were mixed. Two small studies (n=16 in each study) found that enriched protein lead to greater improvement in PUs compared with protein alone or a normal diet.[44, 46] Two studies that compared protein supplemented diets to normal diets and wound care had conflicting findings with one[47] finding that the PUs healed faster in NH residents who consumed more protein and were followed for 8 weeks while another study[49] found no significant difference in hospital patients followed for 1 week who received protein or protein and wound care compared with patients who received wound care or normal hospital care. The poor-quality observational study was of patients with PU who were given nutritional supplements and found that wound volume decreased for patients with prealbumin greater than 9.0 mg/dL while PU volume increased for patients with lower levels. This difference was statistically significant.[53]

Table 6. Nutrition therapy: Protein or amino acid supplementation

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/ Followup	Interventions/ Comparators	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Barnes 2007[53] Quality: Poor N=28 Setting: Hospital	Stage III-IV	Age: Not reported Female: Not reported Population: malnourished	≥30 days	Oral or enteral nutrition support to raise prealbumin levels; concurrent with multiple wound healing interventions (debridement, topical, dressings)	Wound reduction per day: 0.82cc for prealbumin levels > 9.0 mg/dL vs. 0.02cc increase for prealbumin levels < 9.0 mg/dL p<0.03	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/ Followup	Interventions/ Comparators	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Benati 2001[44] Quality: Poor N=16 Hospital	Stage not reported Scores of 13 to 65 On Pressure Score Status Tool	Age: 72- 91 (range) Female: 44% Population: Severe cognitive Impairment	2 weeks	Normal hospital diet vs. high protein supplement vs. high protein enriched with arginine, zinc and antioxidants	Change in PSST score: day 0, 5, 10 and 15. Authors conclude greater improvement in PSST scores in the enriched protein group (represented graphical, numeric data not provided; no test of different)	~
Breslow 1993[54] Quality: Good N=48/28 Setting: Nursing home (long-term care)	Stage II, III, IV	Age: 72 Female: 57% Population: mal-nourished	8 weeks	Treatment A: Oral or enteral nutrition supplement, 14% protein Treatment B: Oral or enteral nutrition supplement, 24% protein	Change in mean wound surface area: 24% protein -4.2 cm^2 for all ulcers; -7.6 for stage IV (both significant) 14% protein -2.1 cm^2 for all ulcers; -3.2 for stage IV (not significant)	+
Brewer 2010[55] Quality: Fair N=35 Setting: Community	Stage II, III, IV	Age: 51 Female: 3% Population: Spinal cord injury	10 months	Daily supplement of 9 mg of arginine (essential amino acid);	Mean ulcer healing times 10.5 +/- 1.3 weeks vs. 21 =/- 3.7 weeks p<0.05	+
Desneves 2005[46] Quality: Poor (trial) N=16 Setting: Hospital	Stage II, III and IV	Mean Age: 73 Female: 38% Population: Elderly	3 weeks	Diet A: Standard hospital diet Diet B: Standard hospital diet plus high-protein, high-energy supplement Diet C: Standard hospital diet plus arginine supplement	PUSH score at 3 weeks: Diet A: 7.0+/1 1.5 Diet B: 6.0 +/- 1.2 Diet C: 2.6 =/- 0.6 (lower is better) p<0.05 Estimate time to complete healing: 15.6 weeks vs. 14.8 weeks vs. 5 weeks	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/ Followup	Interventions/ Comparators	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Lee 2006[47] Quality: Poor (trial) N=71 Setting: Long-term care facilities	Stage II, III or IV	Age: Not reported Female: Not reported Population: residents of long term care	8 weeks	Standard care plus concentrated, fortified, collagen protein hydrolysate supplement, 3/day vs. Standard care plus placebo, 3/day	Treatment group showed about twice the rate of healing compared with comparator group. Reduction in PUSH tool scores: 5.56 (60%) for standard care plus supplement vs. 2.85 (48%)for standard care plus supplement; p<0.05	+
Meaume 2009[48] Quality: Fair (trial) N=160 Setting: Hospital	Stage II or III	Age: 81 Female: 57% Population: Elderly,	6 weeks	Ornithine alpha-ketoglutarate (amino acid salt, precursor of glutamine, arginine, polyamines), 10 g/day vs. Placebo	Baseline area ≤ 8 cm^2 Wound area: -2.3 +/- 4.2 cm^2 vs. -1.7 =/- 1.7; p=0.0006 Closure rate -0.07 cm^2/day vs. 0.4; p=0.0007 Baseline > 8 cm^2: no significant differences	+
Myers 1990[49] Quality: Poor (trial) N=80 Setting: Hospital	Stage I-IV	Age: 70 Female: 43% Population: General	7 days	Group 1: Wound care Group 2: Nutritional support Group 3: Wound care and nutritional support Group 4: Standard hospital care	Wound surface area, mean change in ulcer size: 2.76 mm vs. 2.6 mm vs. 2.34 mm vs. 2.7 mm (no difference)	~

Note: NPUAP, National Pressure Ulcer Advisory Panel.
++ Complete wound healing.
+ Some improvement.
~ No difference.

Specific nutrient supplementation compared with high or low dose or placebo

Two studies *of specific nutrient supplementation* were included, one that assessed the efficacy of ascorbic acid (vitamin C) and one study on the relationship of zinc and ulcer healing. Given the different interventions and moderate size (n=68 and n=79) there is insufficient evidence on which to base any conclusion about nutrient supplementation as a treatment for PUs.

One good-quality study among patients with stage II and stage III ulcers found no significant difference in wound healing or wound surface area reduction between high dose vitamin C compared with low dose C.[51] This study was conducted to replicate an older (1974)[61] and often cited study that reported a significant reduction in ulcer size in patients receiving vitamin compared with placebo.

The one fair-quality observational study comparing oral zinc supplementation to placebo found no significant wound healing benefit in patients with stage II ulcers although a wound healing benefit was reported for patients with stage III and IV ulcers.[56]

Table 7. Nutrition therapy: Vitamin supplementation with vitamin C or zinc

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/ Followup	Interventions/ Comparators	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Houston 2001[56] Quality: Fair N=68 Setting: Nursing home (long-term care)	Stage II-IV	Age: Not reported Female: Not reported Population: Elderly	30 days	440 mg/ayd zinc sulfate vs. similar care without zinc sulfate supplementation	Wound healing: greater improvement in volume in Stage III and IV, not Stage II; No difference in is surface area or complete closure	~
ter Riet[51a] Quality: Good N=88/67 Setting: Nursing home/hospital [a] A 1971 trial, Taylor also evaluated Vitamin C but did not meet the inclusion criteria because of our 1985 cut off	Stage II and III	Age: Not reported Female: Not reported Population: residents of 11 nursing homes and patients in 1 hospital	12 weeks	Ascorbic acid supplementation, 500 mg twice daily vs. Ascorbic acid, 10 mg twice daily	Mean wound surface area reduction per week: 13.88% vs. 22.85% Wound survival curves (projected time to healing) Neither significantly different	~

Note: NPUAP, National Pressure Ulcer Advisory Panel.
++ Complete wound healing.
+ Some improvement.
~ No difference.

Evidence about the Comparative Effectiveness Nutritional Supplementation by Subgroup-analysis (Key Question 1a, 1b, and 1c)

Only 3 of the 15 studies analyzed results by PU characteristics and the impact on the conclusion was inconsistent. One poor-quality study of mixed nutritional supplementation with high calories compared to mixed nutritional supplementation alone stratified the sample by ulcer size and found more improvement in larger ulcers (over the median size of 25.25 cm^2) and no significant improvement in smaller ulcers (below the median area).[50] Another fair-quality trial of amino acid supplementation compared to placebo reported the results by baseline ulcer size and found significantly better results in smaller compared to larger ulcers.[48] The third study

comparing high-dose to low-dose vitamin C examined a subgroup of people with large PUs and found no effect of supplementation on healing, the same result found when the entire study population was analyzed.[51]

None of the included studies examined the impact of patient characteristics or settings.

Nutritional Supplementation: Harms (Key Question 2)

Eight of the 15 studies reported information about harms or adverse events. Three of these were studies of mixed nutritional interventions, three were studies of protein, and two were studies of nutrients. Harms were not always described nor was it always clear whether they were attributed to treatment. The most commonly reported harms were gastrointestinal events and infection. Studies did not always specify whether the harms could be reasonably attributed to the treatment.

In the three of the five studies of mixed or overall nutritional supplementation that reported harms, one study including 50 patients reported study-related adverse events in five controls (16.7 percent) and eight intervention patients (27.6 percent) but these events were not described and the authors report that the difference in the rate of the events is not significantly different for the two groups.[50] Another study of mixed nutritional supplementation reported that none of the 28 patients studied were hospitalized to treat complications of treatment and that the control group had slightly higher occurrence of infection (9 vs. 3 points, $p=0.07$) and greater number of days of antibiotic therapy (103 vs. 36, $p<0.001$).[45] In a study that followed 43 patients, 41 adverse events were reported in 16 patients in the treatment group and 35 events for 13 patients in the control. Most (88 percent) of the events were considered were mild or moderate. Four in the control group were related to treatment (two diarrhea, one nausea, and one vomiting) compared to 9 in the intervention group (six diarrhea, one constipation, and dyspepsia, and one nausea). Differences between the groups were not significant.[52] Three of the eight studies of protein or amino acid supplements reported harms.

In the multicenter trial of amino acid supplementation, involving 160 patients, 33 mild to moderate adverse events were reported for 22 patients (15 in the intervention group and seven in placebo) that were considered related to study medication. Gastrointestinal events were more common in intervention patients, but more serious gastrointestinal events (diarrhea, vomiting and nausea) were evenly distributed with 68 percent of events in the intervention group and 67 percent in the placebo group, suggesting the difference is in mild events. There were 30 serious adverse events were reported during the course of the study, but none were considered treatment related.[48] In a study comparing high and low protein supplementation among 28 patients, recurring mild diarrhea was reported in one patient receiving high protein (24 percent) tube feeding group and mild to severe diarrhea was reported in 1 patient each in the high and lower protein group receiving tube feeding, but no problems were reported for any patients receiving oral nutrition.[54] Another study of protein supplementation that included 71 patients reported reasons for study discontinuation by 11 patients (two hip fractures, three change in renal lab values; four nausea or distention, and two patients died) and added that there was no significant difference in events for the intervention and comparison group but did not discuss whether these reasons were related to the treatment.[47]

Both of the studies of nutrients addressed harms. One study[51] mentioned only that no side effects were reported, but did not specify what adverse effects were measured. The study of zinc sulfate[56] reported that the odds of patients having an infection requiring antibiotics were 7.8 times greater ($p<0.009$) in the intervention group. Also the odds were 12.5 times greater ($p<0.02$)

that these patients would experience nausea/vomiting, though this seemed to be reduced when a low dose vitamin/mineral supplement was added. These negative effects could not be explained by differences in diabetes or energy intake across the groups.

Evidence about the Harms Related to Nutritional Supplementation by Subgroups According to PU Characteristics (Key Question 2a), Patient Characteristics (Key Question 2b), or Setting (Key Question 2c)

No studies reported subgroup analyses to evaluate harms by ulcer, patient, or setting characteristics.

Effectiveness of Local Wound Applications

Wound dressings are a mainstay of pressure ulcer treatment. Dressings serve multiple functions, including padding and protection of the ulcer from pressure and friction, providing a moist wound environment and protection against drying, serving as a barrier in patients with incontinence or other sources of wound contamination, absorbing wound exudate, and promoting autolytic debridement of necrotic tissue and slough. Topical ointments and other therapies such as fibrinolytic enzymes and antimicrobial agents are also used in pressure ulcer management to provide moisture, promote tissue debridement, and eliminate or prevent infection. Finally, biological agents, particularly cellular growth factors, are used to enhance pressure ulcer healing by promoting angiogenesis, epithelialization, and connective tissue deposition.

Different types of local wound applications have different primary functions and the choice of a particular therapy or combination of therapies is often guided by the features and severity of the ulcer. For many pressure ulcers, however, there is more than a single therapeutic need (e.g., exudate absorption, tissue debridement, moist environment), and the most appropriate choice of dressing or topical therapies is not always clear. The harms of different treatments also differ. Studies have therefore compared the effectiveness and harms of different local wound applications for pressure ulcers.

Description of Studies

We identified two systematic reviews and 83 original studies, reported in 87 articles published between 1985 and 2011, examining the effectiveness and/or harms of local wound applications for pressure ulcers in a total of 6,862 patients. Seventy-seven of the original studies were clinical trials. Of these, 14 were rated as good-quality studies, 21 as fair, and 41 as poor. Sample sizes in the trials ranged from 10 to 168 patients. There were six observational studies, including two cohort studies with concurrent intervention and control groups, one pre-post intervention study, and three studies describing outcomes of a single series of patients who all received the same intervention. One cohort study was rated as fair quality; the other observational studies were poor quality.

The *populations* in most studies were elderly patients (mean age typically between 70 and 85) with 11 studies including patients with spinal cord injury (SCI) who were typically younger (mean age between 30 and 50). There was a relatively even distribution of men and women across studies, except in the SCI populations, which were predominantly men. Patient race and ethnicity were infrequently reported. Most studies included NPUAP stage II and III ulcers, except for studies of biological agents, in which most patients had stage III and IV ulcers. Ulcer sites varied widely but most commonly included the sacrum, trochanter, ischium, buttocks, and heel.

The *interventions* studied included a wide range of dressings, topical treatments, and biological agents.

- Dressings come in a variety of forms and serve various functions. Dressings within a given category vary in design and composition but generally have several common features.
    - Hydrocolloid dressings were the most commonly studied. These are adhesive wafers that absorb wound fluid to form a gelatinous mass that conforms to the wound and creates a protective and moist wound environment.
    - Hydrogel dressings are moisture-producing and are commonly used to hydrate dry wounds.

    - Transparent films are clear, semipermeable membranes that provide a protective barrier that allows wound visualization and promotes autolytic debridement.
    - Foam and polymeric membrane dressings provide wound padding and protection and absorb exudate.
    - Silicone dressings offer benefits similar to foam dressings but are less adhesive and have the potential to reduce skin damage during dressing changes.
    - Alginates are seaweed-derived dressings that are typically used to absorb large amounts of exudate.
    - Radiant heat dressings are non contact dressings attached to a heating element that provides warmth intended to promote wound healing by increasing capillary blood flow and resistance to infection.
    - Gauze dressings are fabrics used to protect wounds and provide a wet or dry wound environment and are often used in conjunction with topical solutions and ointments. Gauze dressings are often considered conventional care and used as the comparator in studies of other types of dressings.
- A wide variety of topical ointments and solutions have been used in the treatment of pressure ulcers. Common topical therapies include antimicrobials, enzymes promoting tissue debridement, polymeric pastes (e.g., dextranomer) that absorb wound exudate, and phenytoin, which is thought to promote wound healing through a variety of mechanisms.
- Biological agents include primarily cellular growth factors, most notably platelet-derived and fibroblast-derived growth factors.

Cointerventions were variably reported. In studies that did report them, cointerventions applied to intervention and comparator groups most often included debridement, saline cleansing, pressure-relieving surfaces, and repositioning.

The *comparators* in most studies of dressings and topical treatments were other dressings and/or topical treatments. Some studies used "usual" or "conventional" care as the comparison group, which typically included moist gauze dressings but in some cases was not described. For most studies of biological agents, the comparison group received a placebo.

The *outcomes* reported in most studies included complete wound healing, time to complete healing, and/or reduction in wound surface area or volume. Few studies reported pain reduction or wound infection as an outcome, and no studies reported on infectious complications such as osteomyelitis or sepsis. Most studies did not report harms of treatment. Harms that were reported included dermatologic complications such as rash or skin maceration, hypergranulation, wound deterioration, and summative counts of overall adverse events. Some studies reported on costs of care, though the methods used to calculate costs were usually not well described. No studies reported on measures of utilization such as length of hospital or nursing home stay.

The *timing* of studies, in terms of median ulcer duration prior to intervention, was typically 3 weeks to 3 months, though some studies included ulcers with duration of 1 to 2 years. Most interventions lasted 3 to 12 weeks.

The *setting* for these studies included hospitals (n = 37), long-term care facilities (n = 23), wound care clinics (n = 5), and patients' homes (n = 9). Some studies were implemented in a variety of settings. Most studies were conducted in the United States or Europe, although several studies were conducted in other parts of the world.

Key Points

Dressings

- Wound healing was superior with hydrocolloid compared with gauze dressings (10 studies, strength of evidence: low).
- Wound healing outcomes were similar with hydrocolloid and foam dressings (pooled RR 1.10, 95% CI 0.85 to 1.42, I^2=25.4%, p = 0.235) (seven studies, strength of evidence: moderate).
- There was insufficient evidence regarding the comparative effectiveness of hydrogel, transparent film, silicone, and alginate dressings.
- Radiant heat dressings produced more rapid wound healing than other dressings, but there was no evidence of benefit in terms of complete wound healing (pooled RR 1.23, 95% CI 0.70 to 2.14, I^2 = 0.0% p=0.916) (four studies, strength of evidence: moderate).

Topical Therapies

- There was insufficient evidence about the effectiveness of collagenase and other debriding enzymes in improving wound healing (five studies, strength of evidence: insufficient).
- Three studies of the effectiveness of topical phenytoin used different comparators and produced inconsistent results (strength of evidence: insufficient).
- Dextranomer paste was inferior to wound dressings (alginate, hydrogel) in promoting wound area reduction (two studies, strength of evidence: low).
- Wound healing was similar with topical collagen compared with hydrocolloid dressings or standard care (three studies, strength of evidence: low).

Biological Agents

- Platelet-derived growth factor was superior to placebo in the healing of stage III and IV pressure ulcers (three studies, strength of evidence: low).
- There was insufficient evidence about the effectiveness of other biological agents used for the treatment of pressure ulcers.

Harms of Local Wound Applications

- Harms reported with dressings and topical therapies for pressure ulcers most commonly included skin irritation and inflammation and tissue damage and maceration (31 studies, strength of evidence: moderate). Variability in study populations, interventions, adverse event measurement, and reporting precluded an estimate of adverse event rates for dressings and topical therapies.
- There was insufficient evidence as to whether specific dressing types or topical therapies are associated with fewer harms than others (seven studies).

Subgroups

- Few harms were reported with biological agents (strength of evidence: insufficient).

- There was insufficient evidence about differences in the effectiveness or harms of wound dressings, topical treatments, or biological agents according to ulcer, patient, or setting characteristics.

Detailed Analysis

Our analysis is grouped by key question and placed in subgroups based on comparisons within and across the general categories of wound dressings, topical therapies, biological agents, and conventional care (most commonly gauze dressings).

Evidence about the Comparative Effectiveness of Local Wound Applications (Key Question 1)

Wound Dressings compared with Conventional Care

Studies comparing wound dressings with conventional care are described below and in Table 8.

Hydrocolloid dressings. Ten trials, one good quality,[62] two fair quality,[63, 64] and seven poor quality,[65-71] including a total of 670 patients compared hydrocolloid with gauze dressings, typically saline gauze. Overall, wound healing outcomes were better with hydrocolloid, though several studies found statistically equivalent outcomes between intervention and control groups. We attempted to meta-analyze results from the seven trials reporting complete wound healing as an outcome, but statistical heterogeneity precluded quantitative pooling of results. The single good-quality study reported better rates of complete wound healing with hydrocolloid compared to saline gauze (74 percent vs. 27 percent) over an 8-week timeframe among patients with stage I and II ulcers.[62] The two studies of fair quality included 105 patients and were conducted in hospitals[63] and a long-term care facility.[64] The former study, which included shallow ulcers, found significantly more complete wound healing after 6 weeks with hydrocolloid (see Table 8 below). The latter study, which included stage III ulcers, found no significant difference in complete healing or time to healing between hydrocolloid and saline gauze dressings. Results were similarly mixed in the poor-quality studies, with one[67] reporting significantly better wound healing with hydrocolloid in patients with stage III and IV ulcers.

Hydrogel dressings. Four poor-quality trials[69, 72-74] compared hydrogel dressings with gauze. The poor quality and inconsistency of results across studies limited the ability to draw conclusions. Complete wound healing was significantly better with hydrogel than gauze with iodine (84 percent vs. 54 percent) in one study of hospitalized patients with stage I, II, and III ulcers.[73] The other three studies reported no significant difference.

Foam dressings. Three poor-quality studies provided insufficient evidence about the effectiveness of foam vs. gauze dressings. One poor-quality study among patients with stage II ulcers found greater improvement in Pressure Ulcer Scale for Healing (PUSH) scores with a polymeric foam dressing compared to dry gauze with antibiotic ointment.[75] Two poor-quality trials comparing polyurethane foam dressings to gauze found no significant differences in time to healing[76] or complete wound healing.[77] Both studies reported lower overall costs with foam dressings, attributable to fewer dressing changes and consequently less personnel time.

Transparent film dressings. One fair-quality and two poor-quality trials provided inconsistent results about the effectiveness of transparent film dressings. The fair-quality trial[78] found more complete wound healing over 8 weeks, with a transparent moisture vapor permeable (MVP) dressing compared with saline gauze (64 percent vs. 0 percent). The benefits of the MVP

dressing were observed only in less advanced ulcers (Shea grade II but not III). Two poor-quality studies[79, 80] found no significant differences between transparent film (Op-Site) dressings and gauze.

Table 8. Local wound applications: Wound dressings compared with conventional care

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Hydrocolloid Dressings						
Alm 1989[63] Quality: Fair N=56 Setting: Hospitals	Not reported	Age: 83 Female: 75% Population: Long-term ward patients	6 weeks	1. Hydrocolloid 2. Saline gauze	Complete wound healing: (remaining ulcer area at 6 weeks) Hydrocolloid – 0% Saline gauze – 31% (p=0.016) Harms: No adverse events or pain.	++
Chang 1998[65] Quality: Poor N=34 Setting: Hospital	Stage II, III	Age: 58 Female: Not reported Population: Neurological problems or cancer	8 weeks	1. Hydrocolloid (DuoDerm) 2. Saline gauze	No significant difference in surface area change (arm 1, 34% reduction; arm 2, 9% increase). No harms observed in arm 1. One wound infection in arm 2.	~
Colwell 1993[66] Quality: Poor N=70 Setting: Hospital	Stage II, III	Age: 67 Female: 47% Population: General	14 months	1. Hydrocolloid (DuoDerm) 2.Saline gauze	Complete wound healing: Hydrocolloid (DuoDerm) – 22% Saline gauze– 2% Wound area reduction: Hydrocolloid (DuoDerm) 0.73 cm reduction Saline gauze– NA (0.67 cm increase) Harms not reported.	++
Gorse 1987[67] Quality: Poor N=52 Setting: Hospital	NPUAP Stage: III, IV (Shea, II, III and IV)	Age: 70 Female: 0% Population: > 70% non ambulatory	Days of followup: range: 5-40 days	1. Hydrocolloid (DuoDerm) 2. Saline gauze + chloramine-T (Dakin's solution)	Complete wound healing: (Not reported - Table 3 reports healed or healing as completely healed) "Healed or healing": Hydrocolloid (DuoDerm) - 87% Saline gauze + chloramine-T 69% (p=0.026) Treatment days: Hydrocolloid (DuoDerm) -10 days Saline gauze + chloramine-T - 8.7 days	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Kim 1996[68] Quality: Poor N=44 Setting: Rehabilitation department	Stage I, II	Age: 49 Female: 18% Population: General	3 weeks	1. Hydrocolloid (DuoDerm) 2. Wet-to-dry gauze dressing, iodine	No difference in complete healing (arm 1, 81%; arm 2, 78%). Lower overall treatment cost in arm 1. Harms not reported.	~
Mulder 1993[69] Quality: Poor N=67 Setting: Inpatients and outpatients at 3 sites	Stage II, III	Age: 59 Female: 16% Population: General	8 weeks	1. Hydrogel (Clearsite) 2. Hydrocolloid (DuoDerm) 3. Wet-to-moist gauze	No significant differences in weekly wound size change. Harms: inflammation and excoriation in arm 1 (12%); minor irritation and skin sensitivity in arm 2 (14%).	~
Neil 1989[70] Quality: Poor N=65 Setting: Tertiary care facility	NPUAP Stage: III (Shea, II and III)	Age: Not reported Female: Not reported Population: General	15 months	1.Hydrocolloid (Tegasorb) 2. Saline gauze (WTD)	Complete wound healing: Hydrocolloid –50% Saline gauze– 40%, p=NS Wound size reduction (median): Hydrocolloid - 46% Saline gauze - 43 p=NS	+
Hollisaz 2004 [62] Quality: Good N=83 (91) Setting: Long-term care or home	Stage I, II	Age: 37 Female: 0% Population: SCI	8 weeks	1. Hydrocolloid 2. Saline gauze	Complete wound healing (p<0.01): Hydrocolloid – 74% Saline gauze – 27% Harms not reported	++
Winter 1990[71] Quality: Poor N=51 Setting: Inpatient and outpatient	("ordinary vs. difficult" ulcers)	Age: 74 (median) Range: 25-93 years Female: 75% Population: General	12 weeks	1. Hydrocolloid 2. Paraffin gauze	Complete wound healing: Hydrocolloid – 63% Paraffin Gauze – 19% Harms: Not reported	++
Xakellis1992[64] Quality: Fair N=39 Setting: Long-term care	Stage III (Shea, II, III)	Age: 81 Female: 92% Population: General	6 months	1. Hydrocolloid 2. Saline gauze	Complete wound healing: Hydrocolloid – 89% Saline gauze– 86% Healing time: (median time to healing) Hydrocolloid – 9 days Saline gauze– 11 days (p=0.12) Harms: Not reported	~
Hydrogel Dressings						
Kaya 2005[73] Quality: Poor N=27 Setting: Hospital	Stage I, II, III	Age: 33 Female: 11% Population: Spinal cord injury	15 weeks	1. Hydrogel (Coloplast) 2. Saline gauze	Complete wound healing (p=0.04): Hydrogel – 84% Gauze – 54% Harms not reported.	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Matzen 1999[72] Quality: Poor N=32 Setting: Clinic	Stage III, IV	Age: 83 Female: 16% Population: General	12 weeks	1. Hydrogel (Coloplast) 2. Saline gauze	No significant difference in complete healing (arm 1, 29%; arm 2, 0%). Lower ulcer volume and less need for repeat debridement in arm 1. Harms not reported.	~
Mulder 1993[69] Quality: Poor N=67 Setting: Inpatients and outpatients at 3 sites	Stage II, III	Age: 59 Female: 16% Population: General	8 weeks	1. Hydrogel (Clearsite) 2. Hydrocolloid (DuoDerm) 3. Wet-to-moist gauze	No significant differences in weekly wound size change. Harms: inflammation and excoriation in arm 1 (12%); minor irritation and skin sensitivity in arm 2 (14%).	~
Parnell 2005[81] Quality: Poor N=10 Setting: Nursing home	Stage II, III	Age: Not reported Female: Not reported Population: Long term care	12 weeks	1. Pre-post topical hydrogel with endopeptidase enzymes (Hydrovase) + gauze	Complete wound healing (p not reported): Hydrogel – 50% Pre-hydrogel – 0% Harms: none	++
Thomas 1998[74] Quality: Poor N=30 Setting: Community	Stage II, III, IV	Age: 77 Female: 54% Population: Long-term care	10 weeks	1.Topical hydrogel dressing 2. Saline Gauze	Complete wound healing: Topical hydrogel dressing - 63% Saline Gauze - 64% Healing time: No difference in mean time to healing between groups Topical hydrogel dressing - 5.3 weeks Saline Gauze - 5.2 weeks (p=0.87) Harms: (worsening of ulcer, 1 patient in each group) Treatment – 6% Comparator– 7%	~
Foam Dressings						
Kraft 1993[77] Quality: Poor N=38 Setting: Hospital	Stage II, III	Age: 56 Female: Not reported Population: Geriatric and Spinal cord injury	24 weeks	1. Polyurethane foam (Epi-Lock) 2. Saline gauze	Complete wound healing (p not reported): Foam – 42% Gauze – 21% Lower calculated cost in foam group. Harms not reported.	++

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Payne 2009[76] Quality: Poor N=36 Setting: Inpatient, outpatient, long-term care	Stage II	Age: 73 Female: 39% Population: General	4 weeks	1. Polyurethane foam 2. Saline gauze	Median time to healing not different between groups (28 days in both groups). Lower overall cost in foam group. Harms not reported.	~
Yastrub 2004[75] Quality: Poor N=44 Setting: Long-term care	Stage II	Age: Not reported (>65) Female: Not reported Population: Elderly	4 weeks	1. Polymer membrane dressing 2. Dry clean dressing (gauze + antibiotic ointment	Complete wound healing: NR Improvement in wound healing: Polymer membrane dressing – 87% Dry clean dressing – 65.2% Harms not reported.	+
Transparent Film Dressings						
Kurzuk-Howard 1985[79] Quality: Poor N=43 Setting: Hospital	All stages	Age: 77 Female: 70% Population: General	2 weeks	1. Transparent film (Op-Site) 2. Usual care (variable)	Complete wound healing – no difference between groups. Harms not reported.	~
Oleske 1986[80] Quality: Poor N=15 Setting: Hospital	Stage I, II	Age: 69 Female: Not reported Population: General	10 days	1. Transparent film (Op-Site) 2. Saline gauze	Wound surface area reduction (p for comparison not reported): Film – 43% Gauze – 3% Harms not reported.	+
Sebern 1986[78] Sebern 1989 Quality: Fair N=48 Setting: Community	Stage III (Shea II, III)	Age: 74 Female: Not reported Population: Chronic illness, SCI, Neurological disorders	8 weeks	1. Transparent moisture vapor permeable dressing (MVP) 2. Saline gauze	Complete wound healing: MVP – 64 % Saline gauze – 0% Wound area reduction: (median improvement) MVP – 100% Saline gauze – 52% (p<0.05) Harms: (wound deterioration) MVP – 14% Saline gauze – 58%	++

Note: MVP, moisture vapor permeable; NA, not applicable; NPUAP, National Pressure Ulcer Advisory Panel; SCI, spinal cord injury.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Comparisons of Different Wound Dressings

Comparisons of different wound dressings are described below and in Table 9.

Hydrocolloid compared with hydrocolloid. One fair-quality trial[82] found more favorable reductions in wound area (32 percent vs. 17 percent) and pain with a triangular compared with oval hydrocolloid dressing in patients with stage II and III sacral ulcers.

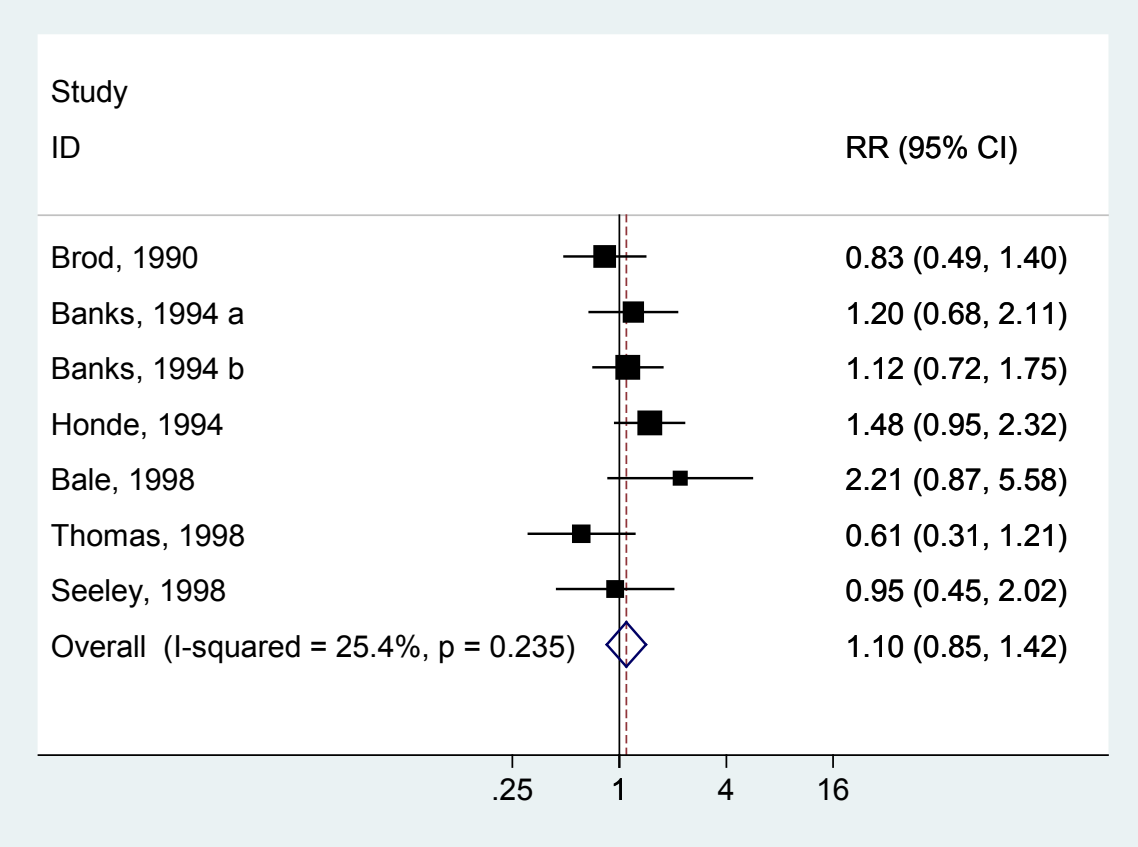
Hydrocolloid compared with hydrogel. Three poor-quality trials compared hydrocolloid to hydrogel dressings and provided insufficient evidence to draw conclusions. One poor-quality trial[83] reported better wound healing (43 percent vs. 24 percent) over 2 months, with hydrogel compared to hydrocolloid dressings in stage I and II ulcers. Two other poor-quality trials[69, 84] found no significant differences in outcomes comparing hydrocolloid and hydrogel dressings in stage II and III ulcers over 8 weeks.

Hydrocolloid compared with transparent film. Only one trial, of fair quality,[85] compared hydrocolloid and transparent film dressings and found no significant difference in wound healing (60 percent in both groups over 8 weeks) among patients with stage II and III ulcers.

Hydrocolloid compared with foam. Three fair-quality[86-88] and four poor-quality[89-92] trials compared hydrocolloid dressings with a variety of different polymeric or hydrocellular foam dressings. Overall the evidence suggested similar wound healing with these two dressing types. One fair-quality study reported similar healing outcomes at 8 weeks but slightly faster time to healing (32 vs. 38 days) with an amino acid copolymer dressing compared with hydrocolloid in patients with stage III and IV ulcers.[87] One poor-quality study reported better complete healing rates (59 percent vs. 27 percent) with a hydrocellular foam dressing compared with hydrocolloid.[91] All other studies reported similar healing outcomes for both dressing types.

We conducted a meta-analysis of the seven studies comparing hydrocolloid with foam dressings. Complete wound healing was similar with foam compared with hydrocolloid dressings (pooled RR 1.10, 95% CI 0.85 to 1.42, I^2=25.4%, p=0.235) (Figure 5). An analysis excluding the four poor-quality trials produced similar results (pooled RR 1.23, 95% CI 0.92 to1.65, I^2=0.0%, p=0.162).

Figure 5. Hydrocolloid dressings compared with foam dressings: Pooled results



Hydrocolloid compared with alginate. A single fair-quality trial[93] compared a strategy of using a calcium alginate dressing for 4 weeks followed by a hydrocolloid dressing for 4 weeks with using the hydrocolloid dressing for all 8 weeks. Complete wound healing was similar across groups but wound area reduction was greater with the alginate/hydrocolloid strategy (69 percent vs. 43 percent).

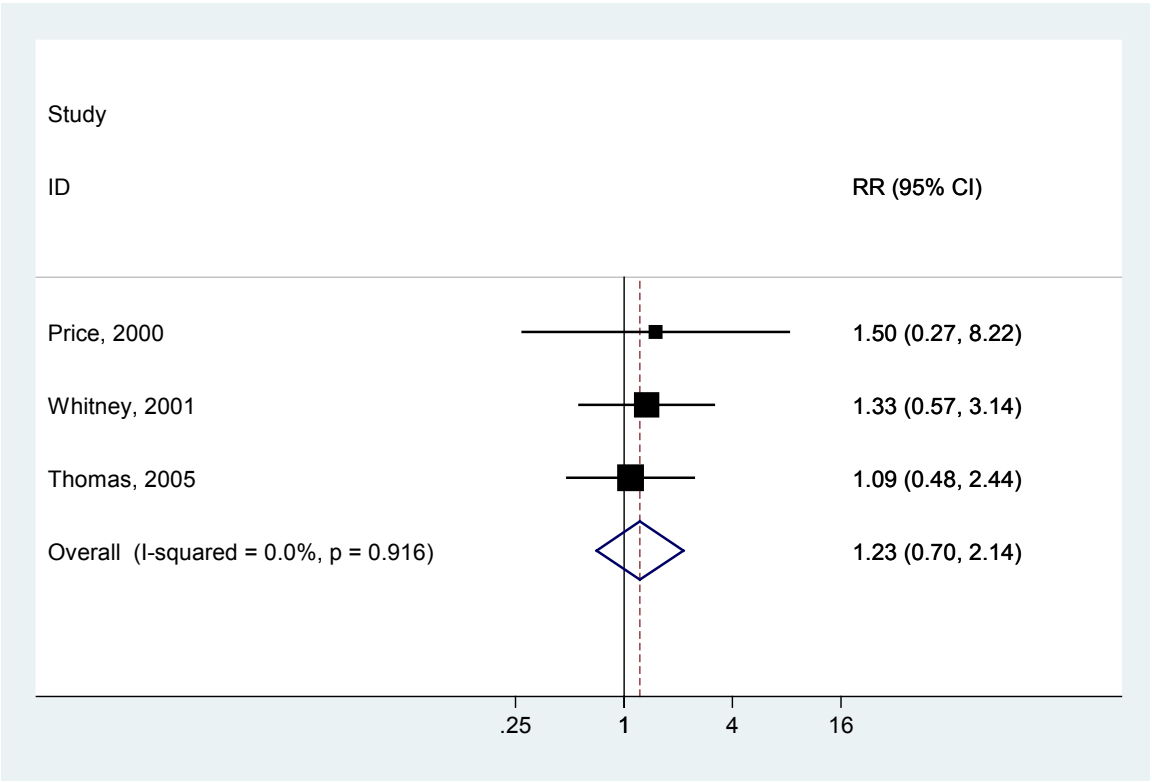
Alginate compared with alginate. A single good-quality trial comparing a silver hydroalginate to a calcium alginate dressing found no significant difference in wound area reduction or infection over 4 weeks but did report faster wound closure rates with the silver-based dressing (0.26 vs. 0.03 cm^2 per day).[94]

Foam compared with silicone. One fair-quality trial[95] and one poor-quality cohort study[96] compared a polymer or hydrocellular foam with a silicone dressing. Wound healing outcomes were similar for foam and silicone dressings in both studies.

Radiant heat compared with other dressings. Two good-quality trials[97, 98] and two fair-quality trials[99, 100] of patients with stage III or IV ulcers compared a radiant heat dressing to hydrocolloid dressings,[97] alginate dressings,[98] or "standard care,"[99, 100] which included a variety of other dressings, including gauze, alginates, foam, hydrocolloids, and hydrogels. Overall, these studies indicated that radiant heat dressings accelerate the rate of healing compared with other types of dressings. One good-quality and two fair-quality studies measured rates of wound closure and found faster healing rates with radiant heat over periods of 4 to 8 weeks. A meta-

analysis of the three trials reporting complete wound healing results indicated similar outcomes with radiant heat compared to other dressings (pooled RR 1.23, 95% CI 0.70 to 2.14, $I^2 = 0.0\%$ p=0.916) (Figure 6).

Figure 6. Radiant heat compared with other dressings: Pooled results



Other comparisons. Several studies evaluated dressings that did not fall into the general dressing categories listed above. A good-quality trial[101] compared an activated charcoal dressing with a hydrocolloid dressing and found no significant difference in healing outcomes among patients with stage III ulcers. Another good-quality trial[102] compared "advanced" wound dressings, including hydrogel, foam, or transparent film, with "standard" dressings, including gauze, alginates, or hydrocolloids. Specific dressings were chosen based on ulcer characteristics. In 58 community-dwelling patients, complete healing was 54 percent in the advanced dressing group and 30 percent in the standard group, though this difference was not significant. A fair-quality trial[103] compared a honey dressing with a bactericidal dressing and found significantly more complete healing (20 percent vs. 0 percent) and better PUSH scores with the honey dressing over a 5-week period.

Table 9. Local wound applications: Comparisons of different wound dressings

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Hydrocolloid vs. Hydrocolloid						
Day 1995[82] Quality: Fair N=96 Setting: Hospital (acute care)	Stage II, III	Age: 75 Female: 49% Population: Elderly, poor health	10 treatment days (mean)	1. Hydrocolloid triangle dressing 2. Hydrocolloid oval	Complete wound healing: Hydrocolloid triangle dressing - 36% Hydrocolloid oval - 22% Wound area reduction (width): Hydrocolloid triangle dressing - 32% Hydrocolloid oval - 17% (p=0.034) Wound area reduction (length): Hydrocolloid triangle dressing - 28% Hydrocolloid oval - 24% (non significant p value) Reduction in pain: (baseline vs. final) Hydrocolloid triangle dressing - 47% vs. 18% Hydrocolloid oval - 39% vs. 32% Pain higher at final assessment in oval group (p=0.04) Harms related to treatment: (Wound deterioration) Hydrocolloid triangle dressing - 4% Hydrocolloid oval - 31% (erythema, severe pain, increase in necrotic tissue, wound size, and depth) Hydrocolloid triangle dressing - 4% Hydrocolloid oval - 31%	**+** (triangle dressing superior)

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Hydrocolloid vs. Hydrogel						
Darkovich 1990[83] Quality: Poor N=90 Setting: Acute and long-term care	Stage I, II (Enis & Sarmieti) NPUAP Stage: II	Age: 75 Female: 55% Population: General	8.6 weeks (60 days)	1. Hydrogel (BioFilm) 2. Hydrocolloid	Complete wound healing: Hydrogel (BioFilm) – 43% Hydrocolloid– 24% Healing time: (mean treatment days) Hydrogel (BioFilm) – 12 Hydrocolloid– 11.3 Wound area reduction: Hydrogel (BioFilm) – 68% Hydrocolloid– 40% Harms: (wound deterioration) Hydrogel (BioFilm) – 1.5% Hydrocolloid– 10%	++
Motta 1999[84] Quality: Poor N=10 Setting: Home	Stage II, III	Age: 60 Female: 50% Population: General	8 weeks	1. Hydrogel polymer (Flexigel) 2. Hydrocolloid (DuoDerm)	Complete wound healing same in 2 arms (40%). No differences in wound improvement or healing rate. Fewer dressing used (with lower total cost) in arm 1. Harms not reported.	~
Mulder 1993[69] Quality: Poor N=67 Setting: Inpatients and outpatients at 3 sites	Stage II, III	Age: 59 Female: 16% Population: General	8 weeks	1. Hydrogel (Clearsite) 2. Hydrocolloid (DuoDerm) 3. Wet-to-moist gauze	No significant differences in weekly wound size change. Harms: inflammation and excoriation in arm 1 (12%); minor irritation and skin sensitivity in arm 2 (14%).	~
Hydrocolloid vs. Transparent Film						
Brown-Etris 2008[85] Quality: Fair N=72 Setting: Wound care clinics, home, long-term care	Stage II, III	Age: 75 Female: 56% Population: General	8 weeks	1. Acrylic (Tegaderm) 2. Hydrocolloid (DuoDerm)	No difference in complete wound healing (60%, both arms). No adverse events related to dressings.	~
Hydrocolloid vs. Foam						
Bale 1998[91] Quality: Poor N=96 Setting: Community	Stage II, III	Age: 76 Female: 77 Population: General	8 weeks	1.Hydrocolloid dressing 2.Hydrocellular dressing	Complete wound healing: Hydro cellular – 59% Hydrocolloid –27% Harms not reported.	++

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Banks 1994a[89] Quality: Poor N=40 Setting: Community dwelling patients	Stage II, III	Age: 72 Female: 48% Population: General	6 weeks	1. Polyurethane membrane (Spyrosorb) 2. Hydrocolloid (Granuflex)	No difference in complete wound healing (arm 1, 60%; arm 2, 50%). Harms: all in arm 2 – overgranulation (10%), discomfort (10%), wound deterioration (10%).	~
Banks 1994b[86] Quality: Fair N=29 Setting: Hospital	Stage II, III	Age: 73 vs.74 (median) Female: 60% Population: Elderly	6 weeks	1.Semi-permeable polyurethane 2.Hydrocolloid	Complete wound healing: Polyurethane– 77% Hydrocolloid – 70% Harms not reported.	~
Brod 1990[90] Quality: Poor N= 38 Setting: Long-term care	Stage II, III	Age: 86 vs. 82 (median) Female: Not reported Population: Elderly	16 weeks	1.Poly-hema 2.Hydrocolloid (DuoDerm)	Complete wound healing: Poly-hema – 52% Hydrocolloid– 62% (p=0.54) Wound healing time: (median) Poly-hema – 32 days Hydrocolloid– 42 days (p=0.54) Harms not reported.	~
Honde 1994[87] Quality: Fair N=167 Setting: Hospitals	Stage III, IV (Shea II-IV)	Age: 82 Female: 72% Population: Elderly	8 weeks	1. Amino acid copolymer membrane (Inerpan) 2. Hydrocolloid (Comfeel)	Complete wound healing (NS): Polymer – 39% Hydrocolloid – 26% Faster healing time with polymer (32 vs. 38 days). Harms not reported.	+
Seeley 1999[88] Quality: Fair N=39 Setting: Outpatient wound clinic	Stage II, III	Age: 76 Female: 54% Population: General, diabetic & wound clinic patients	8 weeks	1.Hydrocellular dressing 2.Hydrocolloid dressing	Complete wound healing: Hydrocellular - 40% Hydrocolloid - 40% Wound area reduction: Hydro cellular - 50% Hydrocolloid - 52% (p=0.31) Harms: (wound deterioration) Hydro cellular - 1% Hydrocolloid - .5% Adverse incidents (infection, rash or maceration) Hydro cellular - .5% (minus 1 non dressing related) Hydrocolloid - 1%	~

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Thomas 1997[92] Quality: Poor N=99[a] Setting: Community	Stage II, III (Stirling classification)	Age: 77 (overall), 79(pressure ulcers) Female: 70% (overall), 69% (pressure ulcers) Population:	15 days	1. Hydropolymer dressing 2. Hydrocolloid dressing	Complete wound healing: Hydropollymer -33% Hydrocolloid dressing-20% Improved, not healed: Hydropollymer - 47% Hydrocolloid dressing-5 8% Deteriorated: Hydropollymer -14% Hydrocolloid dressing-10% No statistically significant differences between treatment groups. Harms: Adverse events including bleeding, excess granulation, and wound dehydration: Hydropollymer -10 patients Hydrocolloid dressing-7 patients	~
Hydrocolloid vs. Alginate						
Belmin 2002[93] Quality: Fair N=110 Setting: Hospitals	Stage III, IV (Yarkony-Kirk III, IV)	Age:84 Female: 71% Population: Elderly	8 weeks	1. Calcium alginate (UrgoSorb) x 4 weeks then hydrocolloid (Algoplaque) x 4 weeks 2. Hydrocolloid (DuoDerm) x 8 weeks	Complete wound healing (NS): Alginate/hydrocolloid – 5% Hydrocolloid – 15% Wound surface area reduction ($p<0.001$): Alginate/hydrocolloid – 69% Hydrocolloid – 43% Harms (excessive granulation): Alginate/hydrocolloid – 11% Hydrocolloid – 9%	+ (alginate then HC superior to HC alone)

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Alginate vs. Alginate						
Meaume and Vallet 2005[94] Quality: Good N= 28[b] Setting: Multicenter (Hospitals)	Stage NPUAP III, IV	Age: (mean) 74.9 vs. 77.6 Female: 59% vs. 69% Population: general	4 weeks	1.Silver release hydroalginate dressing (Silvercel) 2.Calcium alginate dressing (Algosteril)	Wound reduction at week 4(%): Silvercel – -31%% Algosteril– -13% Healing rate (cm2/day): Silvercel – .26 +/- .32 Algosteril– .03+/- .36 (note: ASEPIS and overall results not stratified by wound type, not includable) Harms: Poor tolerability, but reported in aggregate – leg and pressure ulcers.	+
Foam vs. Silicone						
Meaume 2003[95] Quality: Fair N=38 Setting: Nursing homes	Stage II	Age: 83 Female: 84% Population: Elderly	8 weeks	1. Hydropolymer foam dressing 2. Silicone dressing	Complete wound healing (NS): Polymer – 50% Silicone – 44% Harms: More tissue damage, maceration, leakage in polymer. Adverse events in 15% polymer, 6% silicone	~
Viamontes 2003[96] Quality: Poor N=1891 Setting: Nursing homes	Stage not specified	Age: 83 Female: Not reported Population: General	Mean 71 days	1. Hydrocellular foam dressing 2. Silicone dressing	Complete wound healing (NS): Foam – 53% Silicone – 50% Infection (NS): Foam – 3% Silicone – 9% Harms – skin stripping (NS): Foam – < 1% Silicone – 2%	~
Radiant Heat vs. others						
Kloth 2002[99] Quality: Fair N= 40Setting: Hospital and 7 long-term care facilities	Stage III and IV	Age: 78 Female: 63% Population: General(?)	4 weeks	1.Semi-occlusive heated dressing 2. Standard care	Reduction in mean surface area: Heated dressing – 60.7% Standard care – 19.2% Harms:	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Price 2000[98] Quality: Good N=50 Setting: Multiple (hospital, long-term care, community)	(Bergstrom cited, stage 3, 4)	Age: 73 Female: 64% Population: General	6 weeks	1. Radiant heat dressing 2. Standard care (alginate absorbent dressings)	Complete wound healing: Radiant heat dressing – 6% Standard care – 4 % Wound surface area reduction: (% of initial area) Radiant heat dressing – 75 % Standard care – 40% Healing rate: (time difference to 75% of original area) Radiant heat dressing – 75 % Standard care – 40% Pain reduction: No difference in pain scores (mean, SD) Radiant heat dressing – 16.5, 21.42 Standard care 17.5, 19.72 Harms: No difference reported	+
Thomas 2005[97] Quality: Good N=41 Setting: Long-term care	(III, IV - Lazarus, GS, 1994)	Age: 76 Female: 32% Population: general	12 weeks	1. Radiant heat dressing 2. Hydrocolloid	Complete wound healing: 1. Radiant heat dressing - 57% 2. Hydrocolloid - 44% (p=0.46) Harms not reported.	~
Whitney 2001[100] Quality: Fair N=29 Setting: Multiple: (acute care, community, and long-term care)	Stage III, IV	Age: 58 Female: 38 % Population: Mixed (Diabetes, SCI)	8 weeks	1. Noncontact normothermic wound therapy (heated dressing) 2. Standard care (moisture retentive dressings including alginates with saline gauze, foam, hydrocolloids, or hydrogels)	Complete wound healing: Normothermic wound therapy– 53% Standard care– 43% Healing rate: Linear rate of healing in noncontact normothermic therapy group significantly faster that standard care. (p=0.01) Linear rate of healing (mean) Normothermic wound therapy– 0.012cm^2 per day Standard care– 0.004 cm^2 per day	+

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Other comparisons						
Kerihuel 2010[101] Quality: Good N=60 Setting: Hospitals (inpatients and outpatients)	Stage III (Yarkony IIc, IV)	Age: 81 Female: 76% Population: General	4 weeks	1. Charcoal (Actisorb) 2. Hydrocolloid (DuoDerm)	Wound area reduction (NS): Charcoal – 27% Hydrocolloid – 19% Harms: Charcoal – 7% (infection, pruritus) Hydrocolloid – 16% (maceration/exudation, infection, wound aggravation, overgranulation, eczema)	~
Small 2002[102] Quality: Good N=58 Setting: Community	(Stirling scale, Waterlow 1996 - II, III, IV)	Age: 76.5 vs. 78 (median) Range: 19-97 years Female: 60% Population: Not reported	6 weeks	1. Advanced wound care: Hydrogel dressing Foam dressing Transparent film dressing 2. Standard wound care: Cotton, alginates, gauze, hydrocolloids	Complete wound healing: Advanced wound care - 53.6% Standard care - 30% (all stage II ulcers) No harms reported.	~
Yapucu Gunes 2007[103] Quality: Fair N=36 Setting: Hospital		Age: 66 Female: 35% Population: General	5 weeks	1. Honey dressing 2. Exthoxy-diaminoacridine + nitrofurazone dressing	Complete wound healing: Honey dressing – 20% Exthoxy-diaminoacridine + nitrofurazone dressing – 0% (p< .05) Decrease in ulcer size: (mean) Honey dressing – 56% reduction Exthoxy-diaminoacridine + nitrofurazone dressing – 13% (p< .001) Improved PUSH tool scores: Honey dressing – 6.55 +/- 2.14 Exthoxy-diaminoacridine + nitrofurazone dressing – 12.62 +/- 2.15 (p< 0.001) Harms not reported.	++

Note: NA, not applicable; NS, not significant; NPUAP, National Pressure Ulcer Advisory Panel.
[a] Pressure ulcers only. Including venous ulcers, n=199.
[b] Pressure ulcers only. Including venous ulcers, n=99.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Topical Therapies

Comparisons of topical therapies are described below and in Table 10.

Enzymes. Five trials – one good-quality, three fair-quality, and one poor-quality – evaluated topical debriding enzymes and found that enzymes, particularly collagenase, are associated with improved wound healing and possibly reduced pain. A good-quality trial[104] compared collagenase ointment with a hydrocolloid dressing in patients with stage III ulcers and found no significant difference in ulcer healing but improved pain in the collagenase group. In a fair-quality trial,[105] the same investigators found similar healing outcomes for collagenase applied every 24 hours compared with every 48 hours, though pain outcomes were better with the every 24 hour application. Another fair-quality trial compared collagenase with fibrinolysin plus DNAase and found a non significant difference favoring collagenase in necrotic wound area reduction (47 percent vs. 36 percent). A fair-quality trial[106] found no significant differences in wound healing or wound area reduction when comparing topical collagenase with papain/urea, but necrotic tissue debridement was better with papain/urea. A poor-quality trial[107] reported shorter healing times and more complete healing (92 percent vs. 64 percent) with collagenase compared with hydrocolloid after 16 weeks. A fair-quality trial[108] found non significant differences in wound area reduction when comparing Varidase (streptokinase and streptodornase) with zinc oxide (19 percent vs. 2 percent) over 8 weeks.

Phenytoin. Three studies (one good and two fair) comparing topical phenytoin to other local wound applications provided inconsistent evidence on the effectiveness of phenytoin. A good-quality trial[62] found more complete healing of stage I and II ulcers after 8 weeks with hydrocolloid compared to phenytoin (74 percent vs. 40 percent); this effect was seen primarily in the stage I ulcers. One fair-quality trial[109] found shorter time to complete wound healing for stage II ulcers with phenytoin compared with either a hydrocolloid dressing or topical antibiotic ointment (35 vs. 52 vs. 54 days). Another fair-quality trial[110] reported non significant differences in PUSH scores and wound volume reduction (48 percent vs. 36 percent) with phenytoin solution compared with saline gauze in stage II ulcers.

Dextranomer. Two trials, one good and one poor quality, provided evidence that dextranomer paste may be inferior to other local wound applications. A good-quality trial[111] comparing dextranomer paste to a calcium alginate dressing measured partial healing and wound area reduction after 8 weeks in patients with stage III and IV ulcers and found significantly faster wound surface area reduction with alginate. A poor-quality study[112] found greater wound area reduction with a hydrogel dressing compared with dextranomer paste (35 percent vs. 7 percent) after 3 weeks.

Collagen. Evidence from three trials (two good, one poor) provided evidence that topical collagen is not superior to other local wound applications. A good-quality trial[113] comparing topical collagen to a hydrocolloid dressing found similar wound healing for both treatments (51 percent vs. 50 percent) for stage II and III ulcers over 8 weeks. Another good-quality trial[114] of 24 patients found no significant difference in wound area reduction over 3 weeks between topical collagen and placebo (59 percent vs. 46 percent). A poor-quality trial comparing a collagen and cellulose matrix (Promogran) to petrolatum gauze showed no significant difference in wound healing between treatments (90 percent vs. 70 percent) over 8 weeks.[115]

Antimicrobials. Although topical antimicrobials are commonly used in pressure ulcer treatment, we found few studies in the post 1985 time frame comparing antimicrobials to placebo or other interventions. The three studies we identified evaluated different antimicrobial formulations and provided insufficient evidence to draw conclusions about effectiveness. One

fair-quality trial[109] found similar time to stage II ulcer healing with a triple antibiotic ointment compared with a hydrocolloid dressing (54 vs. 52 days), but inferior to topical phenytoin (35 days). A poor-quality trial[116] with stage I and II ulcers found more complete healing over 4 weeks with oxyquinoline ointment compared with A&D ointment, though this benefit was seen only with stage II ulcers (45 percent vs. 22 percent). Another poor-quality trial[117] found no significant differences in ulcer healing when comparing silver sulfadiazine cream to a silver mesh dressing.

Other. Several topical therapies were evaluated in single trials that provided insufficient evidence to draw conclusions about effectiveness. One good-quality trial[118] found more complete wound healing over 6 months in 22 patients treated with resin salve compared with a hydrocolloid dressing (92 percent vs. 44 percent). A fair-quality trial found greater wound area reduction with a combination of a zinc-based ointment and vitamin A-based spray (Dermagran) compared with either the ointment or spray alone, or to placebo (91 percent vs. 26 percent vs. 7 percent vs. 5 percent), in stage II-IV ulcers over 6 weeks.[119] We identified several single-study evaluations of plant-derived and other non pharmaceutical topical treatments[120-123] but all were small and poor quality. Similarly, evaluations of hyaluronate[124] and ketanserin[125] were limited to single, poor-quality trials, and evaluation of hydrogenated castor oil, and trypsin (BCT) ointment[126] was limited to a single, retrospective cohort study.

Table 10. Local wound applications: Topical therapies

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Enzymes						
Agren 1985[108] Quality: Fair N=28 Setting: Multiple (Hospitals/ outpatient)	Stage III	Age: 84 (median) Female: 71% Population: Elderly	8 weeks	1.Collagenase 2.Fibrinolysin and deoxyribonuclease (DNAse)	Complete wound healing: Not reported Disappearance of necrotic tissue: Varidase – 43% Zinc oxide – 50% Wound area reduction: Varidase – 18.7% Zinc oxide – 2.4% Harms not reported.	~
Alvarez 2000[106] Quality: Fair N=21 Setting: Nursing Home	Stage Partial thickness -II: 1 vs 2 Full thickness -III-IV	Age: median (range): 80 (77-86) vs. 84 (53-90) Female: 50% vs 63.6% Population: Elderly	4 weeks	1. Collagenase debriding ointment 2. Papain urea debriding ointment	Complete wound healing: Overall wound response 1.1 vs 4.5 p<0.01, (0=wound deteriorated, 1=no change, 2=minimal change, 3=average improvement, 4=significant improvement, 5=necrotic tissue resolved. Healing time(mean time to 50% granulation): 28 days vs. 6.8 days % reduction in wound area from baseline (SD)wk4: 33.9(26.17) vs. 55.4 (33.5) Harms: Bacterial count at 4 weeks: log 5.0 CFU/mL vs. log 4.6 CFU/mL	**+ (papain superior)**

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Burgos 2000 [127] Quality: Good N=37 Setting: Hospitals	Stage III	Age: 80 Female: 54% Population: Over 55	12 weeks	1. Collagenase ointment 2. Hydrocolloid	Complete wound healing (NS): Collagenase – 17% Hydrocolloid – 16% Wound area reduction (NS): Collagenase – 44% Hydrocolloid – 28% Pain improved more with collagenase (p=0.001) No significant difference in bacterial colonization or total cost. Harms: Collagenase – 6% (dermatitis) Hydrocolloid – 5% (erythema)	~
Muller 2001 [107] Quality: Poor N=24 (26) Setting: Hospital	(Grade IV, method not reported)	Age: 73 Female: 100% Population: Post-hip surgery	16 weeks	1. Collagenase ointment 2. Hydrocolloid (DuoDerm)	Complete wound healing (p<0.005): Collagenase – 92% Hydrocolloid – 64% Shorter mean time to wound healing with collagenase (10 vs. 14 weeks) Collagenase more cost-effective.	++

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Pullen 2002 [128] Quality: Fair N=135 Setting: Hospital	Stage I, II, IV (Seiler stage 2, 3, or 4)	Age: 79 Female: 51% vs. 47% Population: Elderly	4 weeks	1.Collagenase 2.Fibrinolysin and deoxyribonuclease (DNAse)	Wound debridement: (decrease in necrotic wound area) Collagenase -46.7% Fibrinolysin and deoxyribonuclease (DNAse) -36.1% Slightly better debridement results with collagenase (p=0.11) Harms: (adverse events) Collagenase - 68.2% Fibrinolysin and deoxyribonuclease (DNAse) - 49.3% (no adverse events evaluated as related to study medication)	~
Phenytoin						
Hollisaz 2004 [62] Quality: Good N=83 (91) Setting: Long-term care or home	Stage I, II	Age: 37 Female: 0% Population: SCI	8 weeks	1. Hydrocolloid 2. Phenytoin cream 3. Saline gauze	Complete wound healing (p<0.01): Hydrocolloid – 74% Phenytoin – 40% Saline gauze – 27% H > P and SG for stage I and gluteal; H > SG for stage II and ischial; no difference for sacral Harms not reported	–
Rhodes, 2001 [109] Quality: Fair N=47 Setting: Long-term care	Stage II	Age: 79 vs. 76 Range: 60-101 years Female: 8% Population: Elderly	8 weeks or complete wound healing	1.Topical Phenytoin 2. Collagen Dressing (DuoDerm) 3. Triple antibiotic ointment (TAO)	Time to complete wound healing: (mean) Topical Phenytoin - 35 days Collagen Dressing (DuoDerm) - 52 days Triple antibiotic ointment (TAO) - 54 days Average time to healing for phenytoin group significantly shorter than standard care. (p=0.005) No harms detected	+

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Subbanna 2007 [110] Quality: Fair) N=28 Setting: Hospital	Stage II	Age: 34 vs. 32 (mean) Range: 10-55 Female: 12% Population: SCI	15 days	1. Phenytoin solution 2. Sterile gauze	Complete wound healing: Not reported Slight reduction in PUSH 3.0 score, statistically nonsignificant (p=.26) Phenytoin solution - 19.5 Sterile gauze - 11.4 Ulcer size reduction: Phenytoin solution - 47.8% Sterile gauze - 36.3% (p=0.13) No harms reported.	~
Dextranomer						

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Sayag 1996 [111] Quality: Good N=92 (92) Setting: Long-term care and dermatology centers	Stage III, V (Yarkony III, IV)	Age: 81.9 vs. 80.4 Female: 74% Population: Elderly, limited mobility	8 weeks	1. Calcium alginate 2. Dextranomer	Complete wound healing: Not reported 75% healed at 8 weeks: Calcium alginate – 32% Dextranomer– 13% 40% reduction in wound area: Calcium alginate - 74% Dextranomer – 42% Wound surface area reduction: (mean) Calcium alginate 2.39 cm^2 Dextranomer 0.27 cm^2 ($p<0.001$) Harms: (local adverse events including; infection, hyper granulation, pain, skin irritation, bleeding, pruritus) Calcium alginate– 8% Dextranomer– 33%	–
Colin 1996 [112] Quality: Poor N=135 (135) Setting: Six centers	All stages	Age: 79 Female: 54% Population: General	3 weeks	1. Hydrogel (IntraSite) 2. Dextranomer paste (Debrisan)	Wound area reduction ($p=0.03$): Hydrogel – 35% Dextranomer – 7% Harms: Hydrogel – 1.5% Dextranomer – 6% (1 report of pain)	–
Collagen						
Graumlich 2003 [113] Quality: Good N=65 Setting: Nursing home	Stage II, III	Age: median 83.1 Female: 63% Population: Elderly	8 weeks	1. Topical collagen 2. Hydrocolloid	Complete wound healing: Topical collagen - 51% Hydrocolloid – 50% $p=.89$ Area healed per day: (mm2/day, mean, SD) Topical collagen - 6+/-19 Hydrocolloid - 6+/-16 $p=.94$ No adverse events related to treatment.	~

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Nisi 2005 [115] Quality: Poor N=80 Setting: Hospital, plastic surgery unit	Stage II, III, IV	Age: 45 Female: 34% Population: General	2-8 weeks	1. Protease modulating matrix (collagen + cellulose: Promogran) 2. Daily iodine and saline wash, petrolatum-soaked gauze	No significant difference in complete wound healing (arm 1, 90%; arm 2, 70%). Shorter length of hospitalization in arm 1 vs. 2 (360 vs. 1164 days). No harms (inflammatory or allergic reactions or wound regressions) observed in either arm.	~
Zeron 2007 [114] Quality: Good N=24 Setting: Hospital	Stage not reported	Age: Mean: 79.83 vs. 78.33 (Range: 65-90) Female: 21% Population: Elderly	3 weeks	1. collagen-polyvinylpyrrolidone (clg-pvp) 2.placebo	Reduction in ulcer size (mean): clg-pvp – from 3.4 to 1.14 cm placebo – 2.9 to 1.58 cm p= non-significant	~
Anti-microbials						
Chuangsuwa-nich 2011 [117] Quality: TBD (rated by SS) N=45 Setting: Hospital	Stage NPAUP scale II or IV	Age:62.62+/-20.69 vs. 69.10+/-16.02 Female: 58% Population: mixed (in patients and outpatients)	8 weeks	1.Silver mesh dressing 2.Silver sulfizide cream	Complete wound healing: NR Wound surface area at 8 weeks: Silver Mesh: 7.96 cm2 at week Cream: 18.22 cm2 Healing rate: Silver mesh - 36.95% Cream - 25.06% (p=.5) Harms not reported.	~

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Gerding 1992[116] Quality: Poor N=74 (137) Setting: Long-term care	Stage I Stage II (Shea)	Age: NR Female: NR Population: frail, elderly, chronically ill	28 days or until wound resolution	1.Oxyquinolone-containing ointment (DermaMend) 2. A&D ointment	Complete wound healing: DermaMend – Stage I: 58.5% Stage II: 44.5% A &D – Stage I: 57.1% Stage II: 21.8%, p<0.03 Healing time (days to resolution): DermaMend – Stage I: 6.2 Stage II: 7.8 A &D – Stage I: 7.3 Stage II: 13.0, p<0.05 Harms not reported.	++
Rhodes, 2001 (see above)						
Hindryckx 1990[129] Quality: Poor N=21 (21) Setting: Hospital (Inpatient)	Stage not reported	Age:76 Female: 62% Population: NR	Minimum of 3 weeks up to 8 weeks	1. Silver sulfadiazine cream	Sterilization achieved in 10 patients (by 5 weeks) 18 of 21 patients had positive clinical evaluation of ulcers No adverse reactions observed	NA
Other						
Sipponen 2008[118] NA N=22 Setting: Hospital	(Grade system not reported: II-IV)	Age: Not reported Female: Not reported Population: Not reported	6 months	1. Resin Salve (Norway spruce) 2. Hydrofiber bandage	Complete wound healing: Resin salve – 92% Hydrofiber bandage – 44% (p<0.001) Harms not reported	++

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Plant-derived and other nonpharma-ceutical treatments						
Felzani 2011 [124] Quality: Poor N=50 Setting: Hospital	Stage (EPUAP) I-III	Age: 56 (overall) Female: 58% Population:	15 days	1. Sodium hyaluronate acid 2. Lysine hyaluronate acid	Complete wound healing: stage III: 5/7 ulcers healed, compared to treatment 1 p<0.01 Day 15 (% healed) Sodium hyaluronate acid - Stage 1: 70% Stage 2: 40% Lysine hyaluronate acid -Stage 1: 90%, p<0.05 Stage 2: 70%, p<0.02 Harms not reported.	**++ (lysine superior)**
Hsu 2000 [123] Quality: Poor N=32 Setting: Hospital	Stage Grade 2 or higher (Shea)	Age:68.96+/-9.67 Female: 59% Population: Mixed, general, dementia, & SCI	3 weeks	1.Sheng-Ji-San formula and routine medical care 2. Routine medical care	Complete wound healing: Sheng-Ji-San formula – 5% (1/20) Routine care – 0% Decrease in wound surface area: Sheng-Ji-San formula – 6.71+/-29.37 cm2 to 18.33+/-28.28 cm2, p<0.005 Routine care – **Increased** surface area from 35.09+/-40.35 cm2 to 41.59+/-53.11 cm2, p=not significant Harms not reported.	~
Kuflik 2001 [120] Quality: Poor N=19 (20) Setting: Not reported	Stage I, II	Age: Not reported Female: Not reported Population: Elderly, immobile	6 weeks	1. Resurfix ointment 2. Petrolatum ointment	Complete wound healing (p not reported): Resurfix – 50% Petrolatum – 22% No harms in either arm.	~

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
LeVasseur 1991 [121] Quality: Poor N=21 Setting: Hospital and long-term care	Stage I, II (Shea)	Age: 82.5 vs. 81.5 Female: 52% Population: Elderly	6 weeks	1. F14001(active based cream) 2. Placebo (non-active based cream)	Complete wound healing: Not reported (unclear) Faster healing time with F14001 than placebo: 18 vs. 29 days (p=0.08) Wound area reduction: significant reduction in both treatment and placebo group (p<0.001)	~
Narayanan 2005 [126] Quality: Fair N=861(2014) Setting: Long-term care (nursing home)	Stage I and II	Age:60-90+ Female: 67.1% Population: general	4 weeks	1.BCT ointment (hydrogenated castor oil and trypsin) 2.BCT ointment + other 3.Other ((other includes another topical wound dressing or prescriptive product)	Complete wound healing:(% of patients with wounds healed, adjusted) Treatment groups 1 vs 2 vs 3 Initial stage 1, % patients, 95% CI: 74.3% (47.6%-101.0%) vs 63.7% (44.4%-83.0%) vs 37.4% (27.3% - 47.6%) Initial Stage 2, % patients, 95% CI 53.1% (37.7%-68.5%) vs 37.2% (28.5%-45.9%) vs 37.1% (32.9%-41.4%) Initial stage 1 or 2, % patients, 95% CI (p<0.05 for Group 1 vs 2 or 3) 58.6% (45.8% - 71.4%) vs 42.8% (35.0%-50.7%) vs 37.1% (33.2% to 41.0%) Harms not reported.	++

Author Year Quality Enrolled/ Completed Number (ulcers) Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Shamimi Nouri 2008 [122] Quality: Poor N=18 Setting: Hospital	Stage not reported	Age: 47 Female: 22% Population: Spinal complications, amputation of lower limbs, chronic diseases, fractures due to osteoporosis	2 months	1. Topical semelil 2. Conventional treatment	Wound area reduction ($p < .001$): Semelil –78.3% Usual care – 6.3% No harms in either arm.	+
Tytgat 1988 [125] Quality: Poor N=16 Setting: Not reported	Stage not reported	Age: mean (SEM) (range): 58 (6.36) (36-75) vs 60 (3.15) (48-75) Female: 50% Population: MS patients	3 weeks	1.Ketanserin 2% 2. Placebo	Epithelialization comparison with baseline wk 3, mean (SEM): Ketanserin- 2.3 (0.31), Placebo -1.3 (0.49) p="significant" value NR Reduction in wound area at 3 weeks : Ketanserin- 81% Placebo – 16% Harms: Reports no side effects with ketanserin	+

Note: EPUAP, European Pressure Ulcer Advisory Panel; NPUAP, National Pressure Ulcer Advisory Panel; SCI, spinal cord injury.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Biological Agents

Comparisons of different biological agents are described below and in Table 11.

Four studies (two fair, two poor) compared platelet-derived growth factor (PDGF) or platelet gel compared to placebo and provided evidence of better wound healing with PDGF for stage III and IV ulcers. Two fair-quality trials[130-132] comparing PDGF to placebo in stage III and IV ulcers found higher rates of complete wound healing over 16 weeks (23 percent vs. 0 percent)[130] and wound depth reduction over 4 weeks (86 percent vs. 65 percent) with PDGF. One poor-quality trial[133] found better ulcer volume reduction (71 percent vs. 17 percent) but no significant difference in wound healing (38 percent vs. 14 percent) with PDGF. Comparison of different doses indicated that 100 mcg/g per day produced similar or better results than higher or lower doses. A poor-quality trial of platelet gel for stage III and IV ulcers showed no significant difference in ulcer volume reduction over 14 weeks compared to usual care with alginate or topical antimicrobials.[134]

Other growth factors. Other growth factors were evaluated in single studies that provided insufficient evidence to draw conclusions about effectiveness. A good-quality trial found better wound healing in stage II, III, and IV ulcers with nerve growth factor compared with placebo (44

percent vs. 6 percent) over 14 weeks.[135] A good-quality trial comparing a fibroblast-derived dermal replacement system (Dermagraft) to no dermal replacement found no significant difference in wound healing (11 percent vs. 13 percent), ulcer area or volume reduction, or wound infection in stage III ulcers over 24 weeks.[136] A poor-quality trial of fibroblast growth factor (FGF) did find better partial (> 70 percent) wound healing compared with placebo (60 percent vs. 29 percent) in stage III and IV ulcers over 1 month.[132] Another poor-quality trial found no significant difference in wound healing (75 percent vs. 71 percent) or ulcer volume reduction with FGF compared with placebo. Studies of TGF-beta and GM-CSF were limited to single, poor-quality studies.[137, 138]

Macrophage suspension. Two studies, a good-quality trial and a poor-quality cohort study, provided insufficient evidence to judge the effectiveness of macrophage suspensions in the treatment of pressure ulcers. The good-quality trial comparing injected macrophage suspension to standard care (as prescribed by a wound care team) for stage III and IV ulcers found more complete wound healing in the macrophage-treated group (70 percent vs. 13 percent) with a median healing time of 87 days.[139] The poor-quality cohort study also found more complete wound healing (27 percent vs. 6 percent) with macrophage treatment compared with usual care over 12 months.[140]

Table 11. Local wound applications: Biological agents

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Platelet-Derived Growth Factor						
Mustoe 1994 [133] Quality: Poor N=41 Setting: Nursing homes, hospitals	Stage III, IV	Age: 72 Female: 66% Population: Elderly	4 weeks (5-month followup)	PDGF spray 1. 100 μg/g qd 2. 300 μg/g qd 3. Placebo	Ulcer volume reduction at 4 weeks better with PDGF (arm 1, 71%; arm 2 60%; arm 3, 17%). No significant difference in complete wound healing (arm 1, 38%; arm 2, 21%; arm 3, 14%) at 5 months. Harms not reported.	+
Rees 1999 [130] Quality: Fair N=124 Setting: 14 sites	Stage III, IV	Age: 50 Female: 16% Population: General	16 weeks	PDGF (Becaplermin gel) 1. 100 μg/g qd + placebo qd 2. 300 μg/g qd + placebo qd 3. 100 μg/g bid 4. Placebo bid	Complete and ≥ 90% wound healing improved with arms 1 (23%, 58%) and 2 (19%, 59%) vs. placebo (0%, 29%). Twice daily dosing less effective. Harms (worsening ulcer, infection, sepsis) similar in all arms.	++

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Robson 1992a[141] Robson 1992b;[131] Quality: Fair N=20 Setting: Hospital	Stage III, IV	Age: 21-56 years Female: Not reported Population: Spinal cord injury	28 treatment days (29 day trial)	1. Platelet derived recombinant growth factor BB (rPDGF-BB) 1, 10, or 100 Mg/ml rPDGF-BB 2. Placebo	Complete wound healing: Not reported Reduction in wound depth: (mean [SE]) 100 Mg/ml rPDGF-BB – 14.1 [7.4]% of day 0 depth Placebo– 34.9 [6.7]% of day 0 depth Patients treated with 100 Mg/ml rPDGF-BB had an overall 2 fold decrease in ulcer depth compared to placebo. ($p \leq 0.05$) Wound volume reduction: (mean [SE]) 100 Mg/ml rPDGF-BB – 6.4 [4.0]% of day 0 volume Placebo– 21.8 [5.6]% of day 0 volume No harms reported.	+
Robson 1992c[132] Quality: Poor N=49 Setting: Hospital	Stage: III, IV	Age: 38 Female 20% Population: SCI	30 days	1. Recombinant basic fibroblast growth factor (bFGF) 1, 10, or 5 Mg/cm2 bFGF 2.Placebo	Complete wound healing: Not reported > 70% decrease in wound volume bFGF – 60% Placebo– 29% (p=0.04) No harms reported	+
Scevola 2010[134] Quality: Poor N=13 Setting: Hospital	Stage III, IV	Age: Not reported Female: 23% Population: SCI	14 weeks	1. Allogeneic platelet gel 2. Usual care (iodine or alginate + zinc oxide or silver sulfadiazine)	No difference in ulcer volume reduction or infection. No harms (HCV, HBV, HIV infection) observed in either arm.	~
Other Growth Factors						
Hirshberg 2001[137] Quality: Poor N=14 Setting: Wound care clinic	Stage III, IV	Age: 44 Female: 43% Population: General	16 weeks	TGF-beta gel 1. 1.0 2. 2.5 3. Placebo gel qd	No significant differences in ulcer size, volume, or closure. (Only 8 of 14 patients completed the trial.) Harms not reported.	~

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Landi 2003 [135] Quality: Good N=36 Setting: Nursing home	Stage II, III, IV	Age: 80 Female: 72% Population: General	6 weeks	1. Nerve growth factor (murine) 2. Placebo	Complete wound healing better with NGF (44%) vs. placebo (6%) Greater reduction in ulcer area with NGF (73%) vs. placebo (48%) No harms (systemic or local) observed in either group.	++
Payne 2004 [136] Quality: Good N=34 Setting: 9 centers	Stage: III	Age: 69 Female: 32% Population: General	24 weeks	1. Fibroblast-derived dermal replacement (Dermagraft) 2. No dermal replacement	No difference in complete wound healing (11% vs. 13%), ulcer area reduction (50% vs. 34%), ulcer volume reduction (41% vs. 17%), or wound infections (17% vs. 19%). Withdrawal before study completion high, similar (72% vs. 69%). Similar adverse event rates (42% vs. 58%).	~
Robson 2000; [138] Payne 2001 [142] Quality: Poor N=61 Setting: Hospital	Stage: III, IV	Age: 50 Female: Not reported Population: SCI	35 days (1-year follow-up)	1. GM-CSF qd x 35 days 2. FGF qd x 35 days 3. GM-CSF qd x 10 days, then FGF qd x 25 days 4. Placebo qd x 35 days	At 35 days, no differences in complete wound healing (arm 1, 67%; arm 2, 75%; arm 3, 68%; arm 4, 71%). No differences in ulcer volume reduction (63%, 79%, 56%, 68%). No differences in complete wound healing at 1 year. Harms not reported.	~
Macrophage Suspensions						
Danon 1997 [140] Quality: Poor N=199 Setting: Hospital	All stages	Age: 80 Female: 47% Population: Elderly	12 months	1.Macrophages (one-time application) 2. Usual care (variable dressings and topical applications)	Complete wound healing better in macrophage-treated group (27% vs. 6%). Harms not reported.	++

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Wound Applications Compared	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Zuloff-Shani 2010 [139] Quality: Good N=100 Setting: Hospital	Stage III, IV (EPUAP)	Age: 78 Female: 56% Population: Elderly	12 months	1.clg-pvp 2.placebo	Complete wound healing: (leg ulcer subset) AMS – 69.9% SOC – 18% (p< 0.001) Healing time: (leg ulcer subset) Median AMS – 57 days (range:1-394) SOC – 125 days (range: 26-368) Complete wound healing: All patients (includes diabetic ulcers) Percentage of completely closed wounds significantly better for AMS.(p<0 .001)	++

Note: EPUAP, European Pressure Ulcer Advisory Panel; NPUAP, National Pressure Ulcer Advisory Panel; PDGF, platelet-derived growth factor.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Evidence about the Comparative Effectiveness Local Wound Applications by Subgroup-analysis (Key Question 1a, 1b, and 1c)

Few studies conducted subgroup analyses by ulcer characteristics. A fair-quality trial of transparent moisture vapor permeable (MVP) dressings found that the benefit of those dressings over gauze in patients with stage III ulcers was seen only in the less severe ulcers within that stage.[78] A good-quality study demonstrated better outcomes with hydrocolloid compared with gauze for gluteal and ischial but not sacral ulcers.[62] In that same study, hydrocolloid was superior to phenytoin in stage I but not stage II ulcers and in gluteal but not other ulcers.[62] Another fair-quality study found faster healing with phenytoin compared with hydrocolloid in stage II ulcers. A fair-quality study found that the benefit of radiant heat dressings compared with standard care, in terms of rate of healing, was more prominent with larger (> 5 cm^2) wounds.[99] Another fair-quality trial found that the benefit of radiant heat over standard dressings was observed for both stage III and IV ulcers.[143] A poor-quality study found that the benefit of oxyquinoline ointment over A&D ointment was seen in stage II but not stage I ulcers[116]

A good-quality study comparing macrophage treatment to standard care found similar benefits for macrophage treatment in the entire study sample, those with diabetes, and those with ulcers of the leg compared with other locations.[139]

Indirect comparisons across studies to evaluate the possibility that treatment effectiveness is modified by ulcer, patient, or setting characteristics are limited by the fact that there were relatively few studies evaluating any given treatment comparison and by the fact that aside from ulcer stage and location, patient age and gender, and study setting, few variables were reported

consistently across studies. In the 10 studies comparing hydrocolloid with gauze dressings, there was no clear pattern to suggest variation in findings by ulcer, patient, or setting characteristics. The same is true for other treatment comparisons, all of which had fewer studies.

Local Wound Applications: Harms (Key Question 2)

Harms of local wound applications for pressure ulcers were measured in 36 studies.. Because most studies were small, the rates of harms reported in studies that did measure them and statistical comparisons of harms across treatment groups were not reported. Harms commonly measured and reported included skin irritation and inflammation as well as tissue damage and maceration. Commonly measured but infrequently occurring harms included infection, pain, bleeding, tissue overgranulation, and wound deterioration.

Wound Dressings

Hydrocolloid. Harms were measured in 14 studies evaluating hydrocolloid dressings in samples ranging from 7 to 199 patients.[63, 65, 69, 82, 83, 88, 89, 92, 93, 101, 104, 113, 144, 145] Commonly reported harms included skin reactions (inflammation, erythema), maceration, pain, wound deterioration, and overgranulation, with rates of harms ranging from 0 to 16 percent. In a fair-quality study comparing a triangular with oval hydrocolloid dressing in 96 patients, wound deterioration and skin reactions were observed in 4 percent with the triangular dressing and 31 percent with the oval dressing over 10 days.[82]

Hydrogel. Harms measured in five studies of hydrogel dressings in samples ranging from 10 to 135 patients[69, 74, 81, 83, 112] occurred in 0 to 12 percent of patients and included skin irritation and wound deterioration.

Foam. Harms of foam dressings measured in four trials with sample sizes ranging from 40 to 199 patients[85,88, 89, 92, 95] occurred in 1 to 30 percent and included bleeding, overgranulation, wound deterioration, and maceration and tissue damage. A large, poor-quality cohort study of 1891 patients with 3969 ulcers reported a 3 percent infection rate and less than 1 percent rate of skin stripping with foam dressings.[96]

Transparent film. Harms were measured for transparent film dressings in two studies with sample sizes ranging from 72 to 77 patients.[78, 85] One study reported no harms[85] while the other reported a 14 percent rate of wound deterioration.[78]

Alginate. Harms of alginate dressings measured in four studies with sample sizes ranging from 7 to 110 patients[93, 94, 98, 111, 146] occurred in 0 to 11 percent of patients and included infection, overgranulation, skin irritation, maceration, bleeding, and wound deterioration.

Silicone. In a large poor-quality cohort study of 1891 patients with 3969 ulcers, infections were reported in 9 percent of patients managed with silicone dressings and skin stripping occurred in 2 percent.[96]

Radiant heat. One study including 50 patients reported on skin condition after use of radiant heat dressings.[98] Inflammation occurred in 11 percent and maceration in 4 percent, though similar rates were observed with the use of alginate dressings in that study.

Comparative harms. In most studies reporting harms of dressings, rates were qualitatively similar between treatment arms; most studies were small and did not report statistical testing of differences in harms. A poor-quality study comparing hydrocolloid with hydrogel in 90 patients reported wound deterioration in 10 percent and 1.5 percent respectively,[83] although another poor-quality study reported similar rates of skin complications comparing hydrocolloid to hydrogel dressings (12 percent vs. 14 percent).[69] A poor-quality study with 40 patients found no harms

with hydrocolloid but six adverse outcomes among 20 patients (30 percent) with a polyurethane foam dressing.[89] However, a fair-quality study with 40 patients found similar rates of harms (0.5 to 1 percent) comparing a hydrocolloid with a hydrocellular foam dressing.[88] A fair-quality trial with 38 patients found more tissue damage and maceration with a polymeric foam dressing compared with a silicone dressing.[95] However, a large cohort study with 1891 patients found no significant differences in infection or skin stripping with foam compared with silicone.[96] A study of radiant heat compared with alginate dressings found no significant differences in skin complications.[98]

Topical Therapies

Enzymes. One good-quality and two fair-quality studies evaluating collagenase with sample sizes ranging from 37 to 135 patients reported harms, primarily skin inflammation and necrosis, in 0-6 percent of patients.[104, 105, 128] Harms occurred at the same rate in a study comparing collagenase applied every 24 hours with every 48 hours.[105] A single, fair-quality study evaluating fibrinolysin plus DNAase found no harms attributable to the treatment.[128]

Phenytoin. Two fair-quality studies including a total of 71 patients reported no adverse effects from topical phenytoin.[109, 110]

Dextranomer. In a good-quality trial with 92 patients,[111] harms occurred in 22 percent of patients treated with dextranomer paste and included infection, bleeding, overgranulation, and skin irritation, though most adverse reactions were considered minor and did not necessitate stopping treatment.

Collagen. One good-quality and one poor-quality study with 145 patients reported no adverse events with topical collagen.[113, 115]

Antimicrobials. A fair-quality trial with 45 patients[109] found no adverse events associated with triple antibiotic ointment. A poor-quality series[129] reported no adverse effects of silver sulfadiazine cream in 21 patients.

Biological Agents

Platelet-derived growth factor. One fair-quality and one poor-quality study with 137 patients reported on harms (systemic or local infection, or worsening ulcer) of PDGF and platelet gel and found no significant differences compared with placebo.[130, 134]

Other growth factors. No systemic or local harms were observed in a good-quality study of nerve growth factor with 37 patients.[135] No significant differences were found in overall adverse events in a study of 34 patients comparing fibroblast-derived dermal replacement with usual care.[136] Harms were not measured in studies of other growth factors.

Macrophage suspension. A good-quality trial of macrophage suspension including 100 patients reported no adverse events attributable to treatment.[139]

Evidence about the Harms Related to Local Wound Applications by Subgroups According to PU Characteristics (Key Question 2a), Patient Characteristics (Key Question 2b), or Setting (Key Question 2c)

No studies reported subgroup analyses to evaluate harms by ulcer, patient, or setting characteristics. Indirect comparisons across studies to evaluate differential rates of harm by ulcer, patient, or setting characteristics were not possible due to the inconsistency of harm reporting and the infrequent occurrence of specific adverse events.

Effectiveness of Surgery

Pressure ulcers that have progressed to advanced stages often become chronic and do not completely heal with conservative measures. Surgical debridement and vascularized soft-tissue reconstructions are commonly used when nonhealing is observed or the wound has progressed to an advanced stage despite appropriate conservative management. Frail and debilitated elders and patients with sensory and motor deficits are at greatest risk for developing such advanced grade pressure ulcers. Surgical intervention is generally conducted by plastic and reconstructive surgeons and range from local debridement of necrotic and nonviable tissue in the wound bed to direct closure, skin grafting, and closure with soft tissue flaps. The flap is a section of soft tissue that is placed over the open wound and may be harvested from skin (cutaneous), fascia (fasciocutaneous), or muscle (myocutaneous) from non affected parts of the body. Direct closure is rarely indicated due to high risk of failure from increased tension at the closure site.[147] Skin grafting is generally used for shallow non healing ulcers that have a well-vascularized wound bed. This procedure is also rarely used due to high risk of failure from mechanical strain.[147] Most commonly, soft tissue flaps are harvested and used to surgically close the wound. Ideally, the tissue chosen should have adequate blood supply for healing and adequate thickness to meet the need of the surgical site.[147]

Description of Studies

To determine the effectiveness of surgery in the treatment of pressure ulcers we included controlled trials, observational studies with at least two comparative groups, and intervention series if the population was large and the study was conducted at multiple sites. We found one poor quality trial[148] and one fair quality retrospective intervention series that met our inclusion criteria.[149] Given the paucity of evidence, we expanded our inclusion to retrospective series from a single site if the population was large and provided comparative data. We found an additional three fair quality studies, one with two publications.[150-153] We identified one small (n=27, nPU=37) fair quality single center intervention series of patients treated with a single technique (V-Y hamstring myocutaneous island flap) but analyzed the recurrence rates based on patient characteristics.[154] We considered this study to help address Key Question 1b. The total number of included studies was six, including one trial and five observational studies.

The single trial was small (n=60), whereas the retrospective studies were of moderate size, ranging from 59 to 201 patients accounting for 69 to 380 pressure ulcers. The retrospective studies ranged from 5 to 20 years of followup.

The *populations* in studies of surgical interventions for pressure ulcers included elderly nursing home patients and spinal cord injured or neurologically impaired younger adults, mean ages 34-50. All studies enrolled patients with advanced pressure ulcers, stage III or IV NPUAP equivalent.

The *intervention* for all patients was some form of surgical repair of the pressure ulcer, either through primary closure, or soft tissue flap (cutaneous, fasciocutaneous, or myocutaneous). The one trial compared the use of CO_2 laser with knife or electric knife for wound closure by local transposition of tissue or skin graft.[148] Two studies only considered patients with ischial pressure ulcers[153, 154] and one of these studies only analyzed patients receiving hamstring V-Y musculocutaneous flaps.[154] For other intervention series, different approaches were compared.

The *outcomes* for the trial were operative time, blood loss, infection rate, hospitalization days, and failure rate.[148] The outcomes for intervention series were wound healing, recurrence

rates, and harms including wound dehiscence, infection, reoperative rates, and other complications of the surgery.

The *settings* were hospitals or rehabilitation centers. The single trial was conducted in Argentina. The intervention series were from the US, Canada, Australia, and Japan.

Key Points

- Sacral pressure ulcers have lower recurrence rates after surgery than ischial pressure ulcers (strength of evidence: low).
- Spinal cord injured patients are at greater risk of recurrent pressure ulcer after surgical flap than other patients with pressure ulcers (strength of evidence: low).
- Reoperation due to recurrence or flap failure ranged from 12 to 24 percent (strength of evidence: low).
- Wound dehiscence is more common if bone is removed at time of surgical procedure (strength of evidence: low).
- Ischial sites are associated with greater complications than sacral or trochanteric sites (strength of evidence: low).

Detailed Analysis

Evidence about the Comparative Effectiveness of Surgery (Key Question 1)

Determining the effectiveness of surgical techniques for treatment of pressure ulcers was limited to poor-quality intervention series. One poor quality trial and five fair quality intervention series including a total of 647 patients accounting for 1094 pressure ulcers provided evidence on the effectiveness of surgical techniques to treat stage III or IV pressure ulcers. Overall sacral pressure ulcers have lover recurrence rates than ischial pressure ulcers and spinal cord injured patients are at the greatest risk of recurrence. Evidence is insufficient to draw any conclusions on optimal types of soft tissue flap or how this might vary depending on the anatomical site of the pressure ulcer.

We found only one, poor-quality randomized trial (n=60) comparing one surgical technique with another.[148] CO_2 laser was compared with knife or electric knife for wound closure by local transposition of tissue or skin graft.[148] The study reported significant reduction in operative blood loss (2.1 +/- 0.1 cm^3/cm^2 vs. 2.6 +/- 0.1 cm^3/cm^2), operative time (39+/-5 minutes vs. 45 +/- 7 minutes), hospital days (68 percent fewer days), and infection rate (11/30, 37 percent vs. 14/30, 47 percent) with laser surgery. Although the study is poor quality is suggest a laser knife may be superior to standard wound closure.

We found four retrospective series, all rated fair quality, one with two publications, evaluating long-term results of surgeries performed for patients with advanced (primarily stage III-IV) pressure ulcers (n=560, nPU=997).[149-153] Two were conducted at multiple sites[149, 150] and two were conducted at single sites.[151-153] The combined results provide low strength of evidence that sacral pressure ulcers have lower recurrence rates than ischial pressure ulcers and inconclusive evidence to determine optimal surgical procedure.

The smallest retrospective series (n=53, nPU=69) conducted in Japan analyzed outcomes of paraplegic patients, mean age 50 years, treated with fasciocutaneous or myocutaneous flaps over an average followup period of 44 months.[150] It was unclear if the study included all surgically treated patients with ischial or sacral pressure ulcers during the five years of chart review.[150]

There was a trend toward greater recurrence rate in ischial compared with sacral pressure ulcers (50 percent vs. 70 percent) and toward better 36-month pressure ulcer free survival rates with fasciocutaneous compared with myocutaneous flaps (68 percent vs. 43 percent), although the difference was not significant.

Two of the three larger retrospective studies reported on recurrence rate and found overall pressure ulcer recurrence rates of 19 percent[149] and 33 percent.[151] Kierney, et al. was a retrospective study of patients from two centers treated with surgical repair of stage III or IV pressure ulcers between October 1977 and December 1989. They reported on 158 patients with 268 pressure ulcers, mean age 34 to 50 years, with mean followup of 3.7 years. They found that cutaneous flaps had the highest recurrence (12/44, 27 percent) compared with fasciocutaneous (8/54, 15 percent) and myocutaneous flaps (13/99, 13 percent).[149] Sacral sites had the least recurrence (8/69, 12 percent) with similar recurrence rates in ischial and trochanteric sites (32/15, 21 percent and 11/49, 22 percent respectively).[149]

Schryvers, et al. was a single center retrospective study of patients treated with surgical repair of stage III to IV pressure ulcers between 1976 and 1996, with mean followup of 5.3 years for patients with more than three ulcers and 9.3 years for patients with one ulcer.[151] They reported 380 pressure ulcers in 148 patients, mean age 41 years (range: 16-91). The overall ulcer recurrence rate was 33 percent, greatest with ischial ulcers (84/249, 34 percent). Trochanteric ulcers were the slowest to heal (97-105.6 days).Time to complete healing was similar between the different surgical procedures (primary closure 52-97 days, fasciocutaneous flap 52-100 days, myocutaneous 44-105 days).

Foster, et al. evaluated fasciocutaneous and different types of myocutaneous flaps in 201 patients with 280 pressure ulcers, age 50 (range: 16-90), they considered healing at 1 month to be flap success and reported overall flap success of 89 percent (248/280). In patients treated for ischial ulcers, they found that gluteal thigh (fasciocutaneous) and inferior gluteus maximus island (myocutaneous) flaps demonstrated the best healing at 93 and 94 percent while V-Y hamstring and tensor fascia latae flaps (both myocutaneous) had the least success at 58 and 50 percent respectively (Table 12).[152, 153]

Table 12. Surgery: Comparative effectiveness

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Surgical Intervention	Outcomes Measured[a] and Treatment Effect[a]
Foster 1997[153] Quality: Fair n=87/ nPU=112 Setting: Hospital	Stage III-IV ischial	Age: 49 (16-90) Female:26% Population: General (90% spinal cord injury)	10 months (1 month to 9 years)	Myocutaneous flap Fasciocutaneous flap	Healed wound by 1-month post surgery: inferior gluteus maximus island flap 32/34 (94%) vs. inferior gluteal thigh flap 25/27 (93%) vs. V-Y hamstring 7/12 (58%) vs. tensor fascia latae 6/12 (50%)
Foster 1997[152] Quality: Fair n=201/ nPU=280 Setting: Hospital	Stage III-IV pelvic and trochanteric	Age: 50 (16-90) years Female:35% Population: General (90% spinal cord injury)	11.8 month (1 month to 9 years)	Myocutaneous flap Fasciocutaneous flap	Healed wound by 1-month post surgery) 248/280 (89%) Ischial: 94/113 (83%) Sacral: 86/94 (91%) Trochanter 68/73 (93%)

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Surgical Intervention	Outcomes Measured[a] and Treatment Effect[a]
Kierney1997[149] Quality: Fair n=158/ nPU=268 Setting: Hospital	Stage III-IV pelvic and trochanteric	Age 34.5 years Female:22% Population: General (84% spinal cord injury)		Primary closure split-thickness skin graft Cutaneous flap Limberg flap Fasciocutaneous flap Myocutaneous flap Other	Recurrence rates: Overall patient: 25% Overall pressure ulcer: 19% Sacral: 12% Ischial: 21%, Trochanter: 22% FLAPS: Cutaneous 12/44 (27%) Limberg 2/11 (18%) Fasciocutaneous 8/54 (15%) Myocutaneous 13/99 (13%) Spinal cord injured: 20-24% vs. others: 5%
Yamamoto 1997[150] Quality: Fair n=53/ nPU=69 Setting: Hospital	Stage not reported pelvic	Age: 50 (17-75) years Female: 9% Population: Paraplegic	44 months	Fasciocutaneous vs. myocutaneous flap	Recurrence rates: Ischial: 22/45 (48.9% fasciocutaneous 27.8% vs. myocutaneous 63% Sacral: 5/24 (20.8%) fasciocutaneous17.4% vs. myocutaneous 1/1 (100%) Percent PSFS: at 36 months: overall: sacral 70% vs. ischial 50%, NS Ischial: fasciocutaneous 67.5% vs. myocutaneous 42.5%, p=0.055
Schryvers 2000[151] Quality: Fair n=148/ nPU=380 Setting: Hospital (academic)	Stage III-IV (communicate with muscle, bone, or joint) pelvic and trochanteric	Age:41 (16-91) years Female: 22% Population: Spinal cord injury	1976-1996	Primary closure vs. fasciocutaneous vs. myocutaneous flap closure	Complete healing - days from surgery: primary closure n=65, 67.3 d vs. cutaneous/fasciocutaneous n=237, 59.1 days vs. myocutaneous n=86, 82.2 days Recurrence rates: Ischial 84/249 (34%) Sacral 24/82 (29%) Trochanteric 16/90 (18%)

Note: NPUAP, National Pressure Ulcer Advisory Panel; NS, not significant; PUFS, pressure ulcer free survival.
[a] The benefit wound healing category does not apply to surgery because the procedures are all set to fully close the wound.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Evidence about the Comparative Effectiveness of Surgery by Subgroups According to Pressure Ulcer Characteristics (Key Question 1a)

Three retrospective studies considered site of ulcer as risk for recurrence and found that regardless of surgical repair technique, recurrence occurred more commonly in ischial pressure ulcers compared with sacral ulcers.[149-151] There was conflicting evidence on trochanteric ulcers with one study finding a similar recurrence rate as ischial ulcers (22 percent vs. 21 percent),[149]

and one study finding a lower recurrence rate (18 percent vs. 34 percent).[151] Two studies reported on post-surgical healing[151, 155] with one finding that trochanteric surgeries were the slowest to heal[151] and one finding that healing at one month post-surgery was best for trochanteric ulcers (93 percent) compared with sacral or ischial ulcers (83 percent and 91 percent).[152] One study evaluating ischial pressure ulcers considered size of the wound at surgery[153] and found that smaller sized ulcers (average 59.6 cm^2) were less likely to be fully healed at 1 month compared with larger sized ulcers (average 82.9 cm^2), but the authors were uncertain if this was related to sample size differences per group (21 vs. 91) or other risk factors for pressure ulcer. They noted that 71 percent of patients with small ulcers had more than one risk factor for pressure ulcers but did not report this result for patients in the group with large ulcers.[152, 153]

Evidence about the Comparative Effectiveness of Surgery by Subgroups According to Patient Characteristics (Key Question 1b)

Most studies enrolled neurologically compromised patients, primarily spinal cord injured through trauma, tumor, or congenitally, with the average age 34 to 50 years. One study compared recurrence rates among patients with spinal cord impairment and among other patients and found no significant difference between paraplegia (38/160, 24 percent), quadriplegia (7/35, 20 percent), and spina bifida (3/13, 23 percent); however, spinal cord injured patients had a higher risk of recurrence compared with patients with multiple sclerosis (0/9, 0 percent) or other conditions causing immobility (3/51, 6 percent).[149] One small (n=27, nPU=37) single-center retrospective study[154]of patients treated with a single technique (V-Y hamstring myocutaneous island flap) examined recurrence rates according to patient characteristics and found that overall patients with paraplegia and nontraumatic spinal cord injury experienced greater recurrence of pressure ulcers (57.1 percent and 66.7 percent) compared with quadriplegia and traumatic spinal cord injury (33.3 percent and 41.2 percent).[154] Of note, recurrence was greatest in male patients with traumatic spinal cord injury (81 percent). The study also reported that the mean age of traumatic spinal cord injured patients without recurrence was 44 years compared with 28 years for those with recurrence suggesting that younger male patients with paraplegia might be at the greatest risk of recurrence.

Evidence about the Comparative Effectiveness of Surgery by Subgroups According to Settings (Key Question 1c)

One study (n=158, nPU=268) reported long-term data on pressure ulcer recurrence when surgical debridement and closure are supplemented with patient rehabilitation and education.[149] The investigators provided a complete perioperative rehabilitation program that included nutrition, social work, physical therapy, wheelchair and mechanical device maintenance, and detailed skin care education. Pressure ulcer recurrence rates were lower than similar long-term studies (19 percent vs. 33 percent to 39 percent), however no study directly compared patients who received this treatment with those who did not.

Surgery: Harms (Key Question 2)

Three retrospective observational studies, one with two publications, reported on harms associated with surgical techniques for the treatment of pressure ulcers.[151-154] One of the studies examined a subset of patients with ischial pressure ulcers also included in the larger study[152, 153]

and one study only examined ischial pressure ulcers treated with V-Y hamstring myocutaneous flap repair.[154] Two of the studies reported overall complication rate ranging from 28 to 37 percent.[151, 152] The most common harm was wound dehiscence. One study (n=148, nPU=380) was a 20-year chart review of all patients treated at a single center with wound closure or flap procedure for advanced pressure ulcers.[151] The mean followup ranged from 5.3 years for those with more than three admissions to 9.3 years of followup for those with one admission. The overall dehiscence rate was 31 percent. The type of procedure influenced the occurrence of wound dehiscence, with myocutaneous flaps causing the greatest incidence of dehiscence at each site (trochanter 17/43, 41 percent; sacral 5/7, 71 percent; ischial 17/43, 39 percent). Rates of dehiscence were higher, most notably at the trochanteric (16/22, 73 percent) and sacral sites (8/14, 57 percent), when bone was excised due to osteomyelitis detected at surgery.[151] One 16-year chart review at a single center (n=201, nPU=280) also reported on wound dehiscence but separated those with slight dehiscence in which the wound had complete healing within 1 month of surgery and those with significant dehiscence that affected the ability for the wound to heal.[152] The review reported 10 percent slight dehiscence (27/280) and 3 percent significant dehiscence (9/280) but did not report analysis based on site or surgical procedure. A subset from this study of repairs to ischial pressure ulcers, the type most commonly associated with recurrence, were analyzed in a different report (n=87, nPU=112).[152] In this smaller cohort there was 14 percent slight dehiscence (16/112) and 4 percent significant dehiscence (5/112).[152] Partial flap necrosis was found in 10 patients (9 percent) who had myocutaneous flaps using tensor fascia latae, gracilis, or V-Y hamstring grafts.[152] One other small study also examined only ischial pressure ulcers treated with V-Y hamstring myocutaneous flap repair.[154] It did not report on flap necrosis or dehiscence but did report a 24.1 percent reoperation due to recurrence.[154] Need for reoperation from the other studies ranged from 12 to 16 percent but these other studies did not analyze based on surgical intervention.[151, 152] Other harms associated with primary closure or flap repair included osteomyelitis or infection (5 percent to 16 percent),[151, 152] donor site graft loss (2 percent),[152] and one case each of intraoperative myocardial infarction, aspiration pneumonia, and deep vein thrombosis.[152]

In summary, there was moderate evidence that complications associated with primary closure or flap repair of advanced pelvic pressure ulcers are common, ranging from 28 to 37 percent, with wound dehiscence being the most common. Wound dehiscence may be more common if bone is removed at the time of surgery. There was insufficient evidence to determine if one type of repair performs better or worse than another or how this is related to site of ulcer. Reoperation due to recurrence or flap failure ranged from 12 to 24 percent.

Evidence about the Harms Related to Surgery by Subgroups According to PU Characteristics (Key Question 2a), Patient Characteristics (Key Question 2b), or Setting (Key Question 2c)

All of the studies reporting on harms associated with surgical techniques for the treatment of pressure ulcers enrolled patients with advanced, stage III-IV, pressure ulcers with a scarcity of evidence on comparative features of the pressure ulcers. One study considered site of pressure ulcer and type of surgical procedure and found greater dehiscence at trochanteric sites (31/90, 35 percent) compared with sacral or ischial sites (25/82, 30 percent and 74/249, 30 percent respectively).[151] The study also considered dehiscence if bone was excised at the time of surgery, indicative of osteomyelitis, and found that rates of dehiscence were higher, most notably at the trochanteric (16/22, 73 percent) and sacral sites (8/14, 57 percent).[151] One study examining a

subset of patients with ischial pressure ulcers found that the overall complication rate, as well as wound dehiscence and partial flap necrosis, were all greater than the overall population.[152, 153] One study (n=27, nPU=37) found the need for reoperation of ischial pressure ulcers treated with V-Y hamstring myocutaneous flap repair to be 24.1 percent,[154] higher than other rates reported for various flap repairs which were 12 to 17 percent.[151, 152]

No studies reported on differences in harms according to patient characteristics, patient care settings or features of patient care settings.

Effectiveness of Adjunctive Therapies

Adjunctive therapies refer to interventions used in the treatment of pressure ulcers that are in addition to standard wound care, where standard care includes pressure relief and local wound applications. The term adjunctive suggests that these are secondary treatments used to complement or enhance the effect of a primary therapeutic modality. Although many of the therapies described as adjunctive are used as standalone treatments, all are used in conjunction with standard wound care including standard dressing and pressure ulcer relief practices. We use the term adjunctive because it has become the standard label for this group of treatments among researchers and clinicians. Adjunctive therapies include electrical stimulation, electromagnetic therapy, light therapy, laser therapy, nonthermic therapy, hydrotherapy, vibration, shock wave, and hyperbaric oxygen.

Description of Studies

We found five systematic reviews (SR) which were used only as background, 32 trials (3 good quality trials, 27 fair quality trials, and two poor quality trials), and two fair quality observational studies evaluating adjunctive therapies that met our inclusion criteria. Sample sizes in the trials ranged from 6 to 198 patients and study duration from 7 days to 16 weeks.

The *populations* varied with many enrolling an elderly general population and others a younger neurologically compromised group. Sizes and stages of pressure ulcers varied across studies.

Interventions included electrical stimulation (10 studies), electromagnetic therapy (two studies, one SR), therapeutic ultrasound (four studies, one SR), negative pressure wound therapy (four studies, one background SR), light therapy (five studies), laser therapy (three studies plus one direct study included in ultrasound), nonthermic therapy (one study), hydrotherapy (one study), vibration (one study), shock wave therapy (one study), and hyperbaric oxygen (one study). Interventions varied in treatment dose, frequency, duration, and set up. All used standard wound care in conjunction with the adjunctive therapy.

The *comparator* was either sham treatment (placebo) or standard care.

The *outcomes* varied across studies, but most evaluated the percent change in wound surface area, complete wound healing, or time to healing as primary or secondary outcomes. Some studies used scales such as the Pressure Ulcer Scale for Healing (PUSH) and Pressure Sore Status Tool.[156] (See Appendix C for NPUAP scale equivalents)

Study *settings* included hospitals or rehabilitation centers, with fewer outpatient clinics and home health. The studies were conducted in the US, Nigeria, India, Israel, Canada, Scandinavia, Serbia, Greece, Netherlands, and Switzerland.

Direct evidence comparing one intervention with another was limited. Our ability to derive indirect evidence from comparisons across studies was also limited due to variability in study population, design, outcomes measured, and sample size.

Key Points

Key Question 1

- Electrical stimulation was beneficial in speeding the rate of healing of stage II, III, and IV pressure ulcers based on one good-quality and eight fair-quality randomized trials (strength of evidence: moderate).

- Evidence about the effect of electrical stimulation on complete wound healing was inconclusive due to heterogeneous findings across studies (strength of evidence: insufficient).
- The most common adverse effect of electrical stimulation was local skin irritation (strength of evidence: low).
- Frail elderly patients experience more adverse events with electrical stimulation compared with a younger population (strength of evidence: low).
- There was no evidence of benefit with electromagnetic therapy in wound healing of stage II, III, or IV pressure ulcers in patients based on three randomized trials (strength of evidence: low).
- There was no evidence of benefit with ultrasound in the outcome of complete wound healing based on two randomized trials (strength of evidence: low).
- There was no evidence of benefit with negative pressure wound therapy in wound healing over 4 to 6 weeks of therapy based on two randomized trials and one observational study (strength of evidence: low).
- There is insufficient evidence about the harms of electromagnetic therapy, ultrasound, and negative pressure wound therapy.
- There was no evidence of benefit with light therapy in complete wound healing based on two randomized trials (strength of evidence: low).
- Light therapy may be beneficial in reducing wound surface area over time compared with standard care or sham light therapy based on five randomized trials (strength of evidence: low).
- Light therapy was not associated with significant adverse events based on four randomized studies (strength of evidence: low).
- There was no evidence of benefit with laser therapy in wound healing based on four randomized trials (strength of evidence: low).
- Short-term use of laser therapy was not associated with significant adverse events or overall withdrawal based on three randomized studies (strength of evidence: low).

Detailed Analysis

Evidence about the Comparative Effectiveness of Adjunctive Therapies (Key Question 1)

Electrical Stimulation

Electrical stimulation therapy is the delivery of direct electric current through the wound bed using surface electrodes. All equipment is designed to provide high-voltage pulsed currents with variable intensity (voltage) and frequency (pulses per second or Hz), with the electrodes either surrounding the wound or with one electrode placed directly on the wound and a second placed at a distant site. Electrical stimulation is believed to promote cell growth and differentiation.

We found no direct evidence comparing electrical stimulation to other interventions for the treatment of pressure ulcers. Nine randomized trials, one good quality[157] and eight fair quality,[158-165] provided evidence regarding the effect of direct electrical stimulation compared with sham treatments for wound healing. Overall, electrical stimulation increased the rate of healing in stage II, III, and IV pressure ulcers; however, the evidence was insufficient to determine its effect on complete wound healing, due to heterogeneity of findings across studies.

Sample sizes ranged from 7 to 80 patients, accounting for 16 to 192 pressure ulcers. Most were of a duration ranging from 20 days to 16 weeks. One 8-week study followed patients to day 147[159] whereas the rest did not follow patients beyond the study duration. Each study enrolled patients with different sizes and stages of pressure ulcers. One study did not report ulcer stage[161] and one reported ulcers as stage II or III but did not report the scale being used.[165] Age and comorbid conditions varied from young paraplegics to frail elders. Interventions varied in treatment dose, frequency, duration, and set up but all used electrical stimulation sham as the comparator. Most studies evaluated the percent change in wound surface area as the primary outcome. A trend of greater reduction in wound surface area in the treatment group was seen across studies except for one study that found no significant difference.[161] In the one study that followed patients for an additional 90 days after treatment, the trend was lost after day 45 with no significant differences noted at the end of followup[159] (Table 13).

Six studies of electrical stimulation evaluated complete wound healing as either a primary or secondary outcome.[157, 159, 162-165] We did not pool the findings of these six studies using meta-analysis because of statistical heterogeneity of results and inconsistent direction of the estimated effect measures of across studies. A small good-quality study of patients with stage II, III, IV, or unstageable ulcers found no significant difference in complete wound healing at 3 months.[157] All stage II ulcers (treatment n=4, sham n=1) completely healed at 3 months. For all other ulcers, there was an increase in the percentage of ulcers completely healed in the treatment group (5/15, 33.3 percent) compared with the sham group (1/14, 7.1 percent) but no statistical difference between groups.[157] Two fair-quality studies also found no significant difference in complete healing.[159, 163] Three fair-quality studies enrolling elderly patients found an increase in complete wound healing in the electrical stimulation group compared with the sham treatment at 4-8 weeks (14/49 [28.9 percent] vs. 11/49 [23.4 percent], 9/9 [100 percent] vs. 0/7 [0 percent], and 25/43 [58 percent] vs. 1/31 [3 percent] respectively).[157, 162, 164, 165] Two of these studies found a high percentage of completely healed ulcers in the treatment group compared with a very low percentage in the sham group, inconsistent with the results of other trials. Of note, the duration of active treatment for most studies (20 days to 90 days) may not have been long enough to allow for complete healing.

In summary, studies did not demonstrate an effect of electrical stimulation on complete wound healing compared with sham treatment but indicated that electrical stimulation may be superior to sham treatment in accelerating the rate of wound healing. These findings are consistent with the findings of two prior systematic reviews of electrical stimulation for pressure ulcers..[7, 166] We did not pool the findings of these six studies using meta-analysis because of statistical heterogeneity of results and inconsistent direction of the estimated effect measures of across studies.

Table 13. Adjunctive therapies: Electrical stimulation

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/Followup	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Ahmad 2008[160] Quality: n=60 nPU = 60 Setting: Not reported	Stage II	Age: 38.5 years Female: 32/60 (53%) Population: Not reported	5 weeks	Wound surface area percent change: 91% vs. 25-28%	+
Adegoke 2001[158] Quality: n=7/6 Setting: Hospital	Stage IV	Age: 44 (22-60) years Sex: Not reported Population: Spinal cord injury	4 weeks/8 weeks	Wound surface area percent change: 22.2% vs. 2.6%	+
Adunsky 2005[159] Quality: n=63/38 Setting: Hospital	Stage III	Age: 71 years Female: 22 (35%) Population: General	8 weeks/day 147	Complete healing day 147: 25.7% vs. 35.7%, NS Mean time to complete closure: 67 vs. 102 , NS	~
Baker 1996[161] Quality: n=80 nPU=192/185 Setting: hospital and outpatient	Stage Not reported	Age: 36 (19-76) years Female: 14/80 (18%) Population: Spinal cord injury	4 weeks	Wound surface area percent change per week: Active A: 36.4 Active B: 29.7 23.3 – 36.4%+/- 4.8-6.2% vs. Sham: 32.7 %, NS	~
Gentzkow 1991[162] Quality: nPU=49 Setting: Hospital and home	Stage III - IV	Age: 62.8 (29-91) years Female: 45% Population: General	4 weeks/8 weeks for safety	Complete healing percent: 49.8% vs. 23.4%	++
Griffin 1991[163] Quality: n=17 Setting: Hospital rehabilitation center	Stage II, III, IV	Age: 29 (10-74) years Mal 100%Population: Spinal cord injury	20 days	Wound surface area percent change: 80% vs. 52% Complete healing: Stage II: 2/2 vs. 2/2 Stage III: 1/5 vs. 0/6 Stage IV: 0/1 vs. 0/1	+
Houghton 2010[157] Quality: n=34 Setting: Home care	Stage II, III, IV	Age: 50 (23-79) years Female: 14/34 (41%) Population: Spinal cord injury	3 months	Wound surface area percent change: 70% vs. 36%, Complete healing: Stage II: complete healing in both groups at 3 months Stage III, IV< or X: 5/15 (33.3%) vs. 1/14 (7.1%), NS	+
Kloth 1988[164] Quality: n=16 Setting: Not reported	Stage IV	Age: 66 (20-89) years Sex: Not reported Population: Intact nervous system	4-16 weeks	Wound surface area percent change: 44.8% vs. 22.6% increase Complete healing: 100% vs. 0%	++

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Duration/Followup	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Wood 1993[165] Quality: n=71 nPU=74 Setting: Acute care or rehabilitation centers	Stage II or III	Age: 75 (25-99) years Female: 30/71 (42%) Population: General	8 weeks	Wound surface area percent change: 80% decrease (72.9% vs. 12.9%) Complete healing: 58% vs. 3%	++

Note: NPUAP, National Pressure Ulcer Advisory Panel; NS, not significant.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Electromagnetic Therapy

Electromagnetic therapy (EMT) is the delivery of energy composed of an electric field and a magnetic field without direct contact on the skin surface. It is theorized that the electromagnetic field alters the cell membrane, potentially promoting transport across the cell membrane, which is thought to promote healing.[167]

We found no direct evidence comparing electromagnetic therapy with other interventions for the treatment of pressure ulcers. We identified three fair quality randomized controlled trials assessing the effectiveness of EMT compared with no EMT or sham EMT in the treatment of stage II or III pressure ulcers.[168-170]

Although there was a trend in the direction of improvement with EMT, no significant difference in measures of wound healing were found. Two of the studies found a trend toward benefit for EMT in complete wound healing (85 percent vs. 0 percent[168] and 87 percent vs. 67 percent[169]) but a previously conducted meta-analysis found that the difference was not significant (RR 10.00 [95% CI 0.70 to 143.06] and 7.00 [95% CI 0.97 to 50.38] respectively).[171] One study[169] reported a lower median time to complete healing with EMT (stage II ulcers: 13 days vs. 31.5 days; stage III ulcers: 43 days vs. no complete healing).[169] The rate of healing is dependent on the initial size of the ulcer which was not balanced between the active treatment group and sham group. Differences in baseline wound area may have introduced bias for this outcome. One fair-quality randomized trial[170] enrolled 12 patients (nPU=24) with neurologic disorders and stage III or IV pressure ulcers, and compared EMT with sham EMT over an average of 30 sessions. No significant difference in improvement of ulcer stage was found between the two groups at the completion of the study (p=0.649).

Therapeutic Ultrasound

Therapeutic ultrasound is the generation of low frequency sound waves transmitted through soft tissue and created when electrical energy causes deformation of a piezoelectric crystal located in a transducer. The ability of the sound waves to travel through tissue depends on characteristics of the ultrasound and the tissues through which it travels. Both thermal and nonthermal effects of ultrasound are theorized to improve wound healing based primarily on in vitro studies.[172]

We found two randomized trials comparing the effectiveness of ultrasound with sham ultrasound (US)[173-175] and one randomized trial comparing the combination of ultrasound and ultraviolet light with laser therapy or standard wound care.[176]

Limited evidence found no significant difference in complete wound healing although a trend toward improvement with US was seen. All trials were small, had different treatment regimens, and different followup periods. The fair-quality randomized study comparing the combination of ultrasound and ultraviolet-C light with laser therapy or standardized wound care enrolled 20 patients comprising 22 wounds and analyzed 16 patients comprising 18 wounds.[176] All patients received standard wound care. Six wounds per group were analyzed after receiving either alternating days of ultrasound or UVC 5 days per week, laser therapy 3 days per week, or no additional intervention. For the outcome of complete wound healing, the US/UVC group showed the fastest healing, averaging 4 weeks (range 2-6 weeks) compared with the control group that averaged 7 weeks (range 4-13) and the laser group that averaged 11 weeks (range 3-20). The mean percentage change per week in wound surface area was 53.5 percent for the US/UVC group, 32.4 percent for the control group, and 23.7 percent for the laser group. Although there was a trend toward benefit with ultrasound, no significant difference in complete wound healing was found between US/UV therapy and laser therapy. Given that there is only one small, underpowered study assessing this comparison, there is insufficient evidence to determine if a difference exists in the comparative effectiveness of the combination of US/UVC compared with laser therapy.

Of the two randomized studies (n=128) comparing ultrasound with sham ultrasound, neither study found a significant difference in the complete healing of wounds (76 percent vs. 47 percent[173] and 40 percent vs. 44 percent[174] and rate of healing. One small pilot study randomized six stage III or IV pressure ulcers in five patients to receive either ultrasound or sham ultrasound.[177] They reported a decrease in wound size in the ultrasound group with no change in the sham group but did not provide specific data to allow comparative analysis for an effect size and therefore do not add to the body of evidence.

Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT) involves the use of devices that provide a vacuum seal to a wound producing a negative pressure.[178] This causes the wound to contract in size while maintaining a moist environment designed to optimize wound healing.[178] The negative pressure applied to the wound removes excess interstitial fluid which reduces concentrations of inhibitory factors while increasing blood flow. This effect as well as the actual disruption of the extracellular matrix of the wound is believed to promote wound healing.[178] The devices include a vacuum pump, drainage tubing, and foam or gauze dressings that are sealed with an adhesive film.

One fair quality 6 week trial compared NPWT to as system of get products in 28 patients and indirect evidence from one fair quality randomized trial and one observational study. There was no evidence of benefit in wound healing was found with NPWT. We found direct evidence from one 6 week fair-quality trial comparing negative pressure wound therapy to a system of wound gel products in 28 patients.[179] Six patients did not complete the study and were not included in analysis. No significant difference was found in complete healing at 6 weeks (NPWT, 2/20 [10 percent] and topical gel, 2/15 [13 percent]). No significant difference was found in reduction of ulcer volume at 6 weeks (NPWT 52 percent and topical gel 42 percent).[179] We found no other direct evidence comparing vacuum assisted devices to other interventions for the treatment of pressure ulcers.

One fair-quality randomized trial[180] and one fair-quality retrospective cohort study[181] compared NPWT with standard wound care in patients with spinal cord injuries and stage III or IV pressure ulcers. The trial randomized 24 patients and analyzed 22 patients and found no significant difference in mean time to 50 percent reduction in wound volume (NPWT 27 days [SD=10 days]; control 28 days, [SD=10 days], p=0.9).[180] The retrospective cohort study used data collected on U.S. veterans. Patients treated with NPWT were matched with patients treated with standard wound care within each participating site based on demographic variables and ulcer surface area on day 1. Ulcers were classified as healing if the WSA decreased and as nonhealing if the WSA increased. No significant differences were found in percentage of patients demonstrating healing (NPWT 70 percent vs. standard care 67 percent) or nonhealing (NPWT 30 percent vs. standard care 33 percent). No significant difference was found for percentage of reduction in wound surface area in those classified as healing (NPWT 43 +/- 22 percent vs. standard care 50 +/- 26 percent).

Light Therapy

Light therapy involves the delivery of electromagnetic energy to the wound surface to promote healing. In the treatment of pressure ulcers, light therapy involves the delivery of energy from the infrared, visible (wavelength 380-760 nm), and ultraviolet spectrums. There are three types of ultraviolet radiation based on the wavelength of the light transmitted. Ultraviolet-A is the longest wavelength and has the ability to penetrate the deepest. It is the most common type of ultraviolet radiation transmitted to the earth's surface and is responsible for immediate tanning effect. Ultraviolet-B is the medium wavelength radiation, able to penetrate to more superficial layers of the skin and is most associated with burning and the development of skin cancers. The shortest wavelength radiation is derived from ultraviolet-C light and is considered the most damaging.[182] Polarized light involves the use of a crystal that causes the visible electromagnetic wave to vibrate in one direction only. A laser is a device that amplifies light and is notable for its high degree of spatial and temporal coherence.[183] We have grouped polarized, infrared, and ultraviolet light, and classified these as light therapy. We have considered laser therapy as an independent class.

We found no direct evidence comparing light therapy with other adjunctive interventions in the treatment of pressure ulcers. We found five fair-quality randomized trials compared light therapy with either sham light therapy or standard care in patients with pressure ulcers of the pelvis or lower extremity.[184-188] Patients were of a general population, pressure ulcer stage I-IV. Studies were 2-12 weeks in duration. All five studies evaluated change in wound surface area or ulcer size while two studies also measured complete healing and time to complete healing.[184, 185]

We found low-strength evidence that light therapy benefit a reduction in wound surface area but no evidence of benefit in complete wound healing. Three studies (n=262) found a significant difference in reduction in ulcer size[184-186, 188] while two studies (n=219) found no significant difference.[184, 187] Both studies that measured complete healing of patients with stage III-IV ulcers (n=327) found no significant difference between those receiving light therapy compared with sham light therapy (34/78 [44 percent] vs. 34/78 [40 percent][184] and 54 percent vs. 60 percent[185]). Similarly, no significant difference was found in time to complete healing in either study.

Table 14. Adjunctive therapies: Light therapy compared with standard wound care or sham light therapy

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Dehlin 2003[184] Quality: n=198/164 Setting: 8 geriatric centers inpatient/outpatient	Stage II-IV	Age: 84 (65-105) years Female: 107/164 (65%) Population: General	12 weeks	Complete healing: 34/78 (43.6%) vs. 34/78 (39.5%), NS Reduction ulcer size: NS Time until total healing: NS	~
Dehlin 2007[185] Quality: n=181/163 Setting:8 geriatric centers inpatient/outpatient	Stage III	Age: 84 (65-105) years Female: 1000/163 (61%) Population: General	12 weeks	Normalized reduction in ulcer size at week 12: 0.79 vs. 0.50, Normalized weekly reduction in ulcer size over time 15.1% vs. 10.9% Rate of normalized reduction in PU size, NS Percent totally healed ulcers: 54.4% vs. 59.5%, NS Time to totally healed ulcers, NS	+
Durovic 2008[186] Quality: n=48/40 Setting: Not reported	Stage I-III	Age: 65 years Female: 18/40 (45%) Population: General	4 weeks	Wound surface area change: 4.29 cm^2 reduction vs. 3.82 cm^2 increase	+
Iordanou 2002[187] Quality: n=55, nPU=2 Setting: Hospital	Stage I-IV	Age: 67.1 years Sex: Not reported Population: General	2 weeks	Wound surface area change: 1.58 cm^2 reduction vs. 0.06 cm^2 reduction, NS	~
Schubert 2001[188] Quality: n=74 eligible/ 67 included/ 59 completed Setting: Hospital	Stage II-III	Age: 85 years Female: 46/72 (64%), Population: General	10 weeks	Wound surface area per week: 29.8% vs. 20.0% Healing rate: 49% higher healing rate for active group, NS	~

Note: NPUAP, National Pressure Ulcer Advisory Panel; NS, not significant; PU, pressure ulcer.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Laser Therapy

We found one randomized trial comparing laser therapy with another adjunctive therapy for the treatment of pressure ulcers[176] and three randomized trials comparing laser therapy with standard wound care, to standard wound care alone, or sham laser therapy (Table 14).[189-191] Trials included 16-86 patients, lasted 5-16 weeks, and used different treatment regimens. Two

studies enrolled an elderly population with stage III ulcers[189, 190] and two enrolled a younger population with spinal cord injuries and stage II-IV pressure ulcers.[176, 191]

We found low-strength evidence that laser therapy did not benefit wound healing. The fair-quality randomized study comparing the combination of ultrasound and ultraviolet-C light with laser therapy or standardized wound care enrolled 20 patients and found faster healing in the US/UVC group (4 weeks) compared with standard therapy (7 weeks) or laser treatment (11 weeks). The mean percentage change per week in wound surface area was 54 percent with US/UVC, 32 percent with standard care, and 24 percent with laser treatment.[176] Although a trend toward benefit with ultrasound, at 12 weeks, no significant difference in complete wound healing was found between US/UV therapy and laser therapy (RR=1.44, 95% CI 0.85 to 2.64).[192]

Two studies (n=102) found no significant difference in reduction in wound size between treatment groups.[189, 190] Two studies (n=124/nPU=143) found no significant difference in complete wound healing.[190, 191] One study found no significant difference in time to complete healing.[191]

Table 15. Adjunctive therapies: Laser therapy compared with standard wound care or sham laser therapy

Author Year Quality Number Enrolled/ Completed Setting	Pressure Ulcer Stage (NPUAP)	Age Sex Population	Followup	Outcomes Measured and Treatment Effect	Benefit: Wound Healing
Lucas 2000[189] Quality: n=16 Setting: Nursing homes	Stage III pelvic and lower extremity	Age: 88 (72-95) years Female: 14/16 (88%) Population: General	6 weeks	**Wound surface area percent change:** 83% vs. 95%, NS	~
Lucas 2003[190] Quality: n=86/79 Setting: Nursing homes	Stage III pelvic and lower extremity	Age: 82 years Female: 54/86 (63%) Population: General	6 weeks	Absolute and relative reduction in wound size: NS Complete wound healing: 18/36 (50%) vs. 15/43 (35%) Wound surface area change: 6/36 (17%) vs. 2/43 (5%) Developed stage IV ulcer**:** 3/37 (8%) vs. 5/44 (11%), p=0.72	~
Taly 2004[191] Quality: n=35, nPU=64 Setting: Hospital rehabilitation ward	Stage II-IV pelvic and lower extremity (2 elbow)	Age: 22 years Female: Not reported Populations: Spinal cord injury	5 weeks	Complete healing**:** 18/35 vs. 14/29, NS, Time to complete healing: 2.45 weeks vs. 1.78 weeks, NS	~

Note: NPUAP, National Pressure Ulcer Advisory Panel; NS, not significant.
++ Complete wound healing.
+ Some improvement in wound healing.
~ No difference.

Other Adjunctive Therapies

Evidence was limited to a single study on vibration therapy,[193] hydrotherapy,[194] extracorporeal shock wave therapy,[195] noncontact normothermic wound therapy,[99] and hyperbaric oxygen.[196] Due to study quality, size, and duration, evidence was insufficient to report on comparative effectiveness of these treatments. We elected to perform an additional search specifically on hyperbaric oxygen at the recommendation of our technical expert panel given that this has been an adjunctive therapy commonly used in the treatment of wounds. Our search revealed no additional studies that met our inclusion criteria. The single study on hyperbaric oxygen from our original search was designed to determine if a synergistic effect occurred with electrical stimulation by comparing hyperbaric oxygen alone with the combination of hyperbaric oxygen and electrical stimulation on the healing rates of stage III or IV pressure ulcers.[196] Subjects were assigned to receive either hyperbaric oxygen alone twice daily or hyperbaric oxygen twice daily and electrical stimulation five days per week. All wounds diminished in size over time, with no significant difference between the two groups.

Evidence about the Comparative Effectiveness of Adjunctive Therapies by Subgroups According to Pressure Ulcer Characteristics (Key Question 1a), Patient Characteristics (Key Question 1b), or Setting (Key Question 1c)

Electrical Stimulation

Most studies of electrical stimulation enrolled patients with pelvic and lower extremity pressure ulcers and did not perform subgroup analysis to determine if a difference existed in treatment effectiveness based on anatomic site. Comparison of the results of electrical stimulation studies by ulcer stage (II, III, and IV) and by patients enrolled did not provide evidence of differential effectiveness by ulcer stage.[157-160, 163, 164]

Most studies enrolled a general population and did not perform subgroup analysis to allow comparison of treatment effectiveness based on unique patient characteristics. Four trials enrolled only patients with spinal cord injuries and the results were consistent with the overall body of evidence.[157, 158, 161, 163] We found similar results in studies that enrolled a younger population (mean age $\leq$ 51 years)[157, 160, 161, 163] compared with an older population (mean age >51 years).[158, 159, 162, 164, 165]

Most studies were conducted in a hospital or rehabilitation center,[158, 159, 163, 165] with one study conducted in a home care setting[157] and the others in a combination of settings[161, 162] or not reported.[160, 164] Findings did not differ based on setting. See Table 15.

Electromagnetic Therapy

One trial of EMT (n=30) randomized patients based on baseline stage of ulcer (II or III) to receive either EMT or sham. There was no significant difference in outcomes between the groups, based on baseline ulcer stage.[169] The two trials of EMT enrolled different patient populations in different settings, but both had similar findings of no significant effect of EMT.[168, 169]

Therapeutic Ultrasound

The two randomized trials comparing ultrasound with sham therapy included a mixed population of hospitalized and nursing home patients of varying stages of pressure ulcers without

subgroup analysis to determine if a difference exists based on features of the pressure ulcer, patient, or care setting.

Negative Pressure Wound Therapy

There was insufficient evidence to determine if the comparative effectiveness of NPWT differed according to features of the pressure ulcers or characteristics of the patient. One retrospective cohort study reported on the effectiveness of patients being treated with NPWT compared with standard wound care in the home care setting.[197] The Outcome Concepts System was used to identify patients being treated at home for pressure ulcers and the study considered the outcomes of acute care hospitalization and emergent care rates between January 1, 2003 and December 31, 2004. Patient characteristics were similar in both groups. Sixty patients were treated with NPWT while 2,288 patients were treated with standard wound care.[197] Of this small group treated with NPWT, a significantly lower percentage of NPWT patients were hospitalized (35 percent vs. 48 percent, $p<0.05$), fewer required emergent care services (0 percent vs. 8 percent, $p<0.01$), and fewer required hospitalization for a wound-related problem (5 percent vs. 14 percent, $p<0.01$).[197] No other study evaluated the outcomes of hospitalization or emergent care needs. Given the small sample size in the NPWT group and given that outcomes of wound healing were not assessed, there was insufficient evidence that NPWT in the home setting provided significant benefit.

Light Therapy

Few studies performed subgroup analysis to determine if treatment strategies differed according to features of the pressure ulcers, patient characteristics, or patient care settings. Two studies performed subgroup analysis to determine if differences in outcomes existed based on body mass index.[184, 185] One study of patients with stage III-IV NPUAP ulcers found a larger reduction in ulcer size for patients with a body mass index <20 (3.3 cm^2 vs. 2.5 cm^2, $p<0.01$)[184] but a subsequent study of stage III NPUAP ulcers found no significant difference in this subgroup.[185]

Laser Therapy

No studies performed subgroup analysis to determine if treatment strategies differed according to features of the pressure ulcers, patient characteristics, or patient care settings. Two studies (n=51/nPU=80) enrolled younger patients with spinal cord injuries and found no evidence of benefit in complete wound healing, consistent with the overall body of evidence that included a mixed population.[176, 191]

Adjunctive Therapies: Harms (Key Question 2)

We found 14 trials and two observational studies evaluating the harms of adjunctive therapies (electrical stimulation [three studies], electromagnetic therapy [one study], ultrasound [three studies], negative pressure [two studies], light therapy [four studies], and laser therapy [three studies]). We found no direct evidence comparing one intervention to another and reporting on comparative harms. Indirect evidence of comparative harms was difficult to derive due to variability in study population, study design, outcomes measured, and sample size.

Electrical Stimulation

Three studies reported on harms associated with the use of direct electrical current in the treatment of pressure ulcers compared with sham electrical stimulation.[157, 159, 162] Overall withdrawal was high in the Adunsky study which enrolled hospitalized frail elders with stage III pressure ulcers in Israel (overall withdrawal 25/63, 40 percent). Fifteen patients withdrew due to adverse events, 11 of 15 (73 percent) in the treatment group, mostly due to clinical (8/15) or ulcer deterioration (4/15). In two other studies, however, withdrawal occurred in only one spinal cord injured patient[157, 162] The most commonly reported adverse event was skin irritation. Adunsky reported two cases of excessive granulation (5.2 percent) and two cases of a local irritation when the current was combined with topical sulphadiazine ointment on the wound, believed to be due to the effect of electrical stimulation on the silver ions in the ointment.[159]

Electromagnetic Therapy

One small randomized study (n=30) reported on adverse effects and reported none.[169]

Therapeutic Ultrasound

Three studies reported on overall withdrawal, which ranged from 12.5 percent to 32.5 percent, mostly due to death or discharge from the care setting and not related to the intervention.[173, 175, 176] One study reported that 2 of 45 patients in the ultrasound group (4.4 percent) complained of pain associated with ultrasound but no other adverse events were reported.[175]

Negative Pressure Wound Therapy

No controlled studies comparing NPWT to standard care reported on harms. One intervention series of 17 patients with sacral ulcers, stage unknown, reported an overall withdrawal of eight (47 percent), three (18 percent) due to death not attributed to the intervention and five (29 percent) due to need for surgery due to incomplete healing. One retrospective cohort study compared patients being treated with NPWT with patients being treated with standard wound care in the home care setting[197] and reported on emergent care or hospitalization for wound infection, deteriorating wound status, or new lesion/ulcer.[197] Compared with patients receiving standard care, a significantly lower percentage of NPWT patients were hospitalized for wound related issues (3/60 [5 percent] vs. 310/2288 [14 percent], $p<0.01$) or required emergent care for wound related issues (0/60 [0 percent] vs. 189/2288 [8 percent], $p<0.01$).[197]

Light Therapy

Four studies reported on overall withdrawal from studies of light therapy, ranging from 17 to 19 percent, with none believed to be directly related to the treatment.[184-186, 188] Two studies specifically evaluated adverse events,[184, 185] with similar number of events occurring in both the

light therapy and the sham light therapy groups, and considered unrelated to the treatment. The most common reported adverse event was tingling or pain in or around the wound (n=12 of 327 patients, 3.7 percent). One patient had bleeding in the wound and one patient reported redness.[184]

Laser Therapy

Four studies compared laser therapy with either standard care or sham laser therapy in the treatment of stage II-IV pressure ulcers.[176, 189-191] No treatment-related adverse events were reported in three studies[176, 189, 190] and one study reported excessive granulation tissue in one of 64 ulcers, the only treatment-related adverse event that was observed.[191] One study evaluated the progression to stage IV ulcers in patients with stage III ulcers and found that during the 6-week study, no significant differences existed between groups in the development of stage IV ulcers (5/44 [11 percent] vs. 337 [8 percent], p=0.72).[190]

Evidence about the Harms Related to Adjunctive Therapies by subgroups according to Pressure Ulcer Characteristics (Key Question 2a), Patient Characteristics (Key Question 2b), or Setting (Key Question 2c)

There was insufficient evidence to determine if differences in harms of any adjunctive therapies exist based on features of the pressure ulcers.

One study of electrical stimulation enrolled hospitalized frail elders with stage III pressure ulcers in Israel and had a high rate of overall withdrawal (25/63, 40 percent) and a high rate of withdrawal due to adverse events (15/63, 24 percent).[159] The two other studies reporting on harms associated with electrical stimulation enrolled younger patients, many of whom had spinal cord injuries, and found a very low overall withdrawal or withdrawal due to adverse events.[157, 162] This difference may be due to the patient age and comorbid features. However, there may have been other differences in treatment delivery, patient populations, or harms assessment that accounted for the observed differences across studies.

There was insufficient evidence to determine if differences existed in harms of any adjunctive therapies based on patient care settings.

Discussion

Treatment for pressure ulcers involves a variety of different modalities intended to: alleviate the conditions contributing to ulcer development (support surfaces, repositioning, nutritional support); protect the wound from contamination, create a clean wound environment, and promote tissue healing (local wound applications, debridement, wound cleansing, and a variety of adjunctive therapies); and surgically repair the wound. We evaluated evidence addressing the comparative effectiveness and harms in treatment categories where significant uncertainty exists about the best therapeutic options: support surfaces, nutritional supplements, local wound applications (dressings, topical therapies, biological agents), surgical interventions, and adjunctive therapies. We also attempted to discern whether the balance of benefits and harms for different treatment options varied according to characteristics of the pressure ulcer, the patient, or the setting in which care was being delivered.

Key Findings and Strength of Evidence

We identified evidence addressing a variety of different support surfaces, including air-fluidized beds, alternating pressure beds and chair cushions, and low air-loss beds. Other types of support surfaces were evaluated only in small, single studies. We found evidence of moderate strength that air-fluidized beds are superior to other support surfaces. Evidence about the effectiveness of alternating pressure surfaces was inconclusive, though among alternating pressure beds, we found moderate-strength evidence that different mattress brands performed similarly. There was moderate-strength evidence that low-air-loss beds do not convey benefit over standard foam mattresses. The harms of different support surface options were minimal.

Studies of nutritional support evaluated increased mixed nutritional supplementation including increased caloric intake and vitamins with or without high protein supplementation, protein or amino acid supplementation using protein or amino acids with or without additional caloric support or vitamin supplementation, and specific nutrient supplementation with vitamins or minerals such as ascorbic acid (vitamin C) or zinc. Studies provided low strength of evidence for a small benefit in wound size reduction and healing time with mixed nutritional supplementation. There was also low strength of evidence indicating no or small benefits in wound healing with protein or amino acid supplementation. Evidence about vitamin supplementation alone was insufficient to draw conclusions.

A wide variety of modern wound dressings have been compared to each other or to standard care, usually with gauze dressings. We found low-strength evidence that hydrocolloid dressings are superior to gauze and moderate-strength evidence that hydrocolloid and foam (hydrocellular or polyurethane) dressings produced similar wound healing results. Evidence about the comparative effectiveness of other dressings – hydrogels, transparent films, silicone, and alginates – was insufficient to draw conclusions. We found moderate-strength evidence from four studies that radiant heat dressings accelerated the rate healing compared to other dressings, but we did not find evidence of a benefit of radiant heat dressings in terms of complete wound healing.

The most commonly evaluated topical therapies were debriding enzymes (primarily collagenase), phenytoin solution, dextranomer paste, and collagen. There was low-strength evidence that dextranomer is less effective than standard wound dressings or other topical agents. Evidence about enzymes and phenytoin was inconsistent, and insufficient to draw conclusions.

Collagen did not appear to provide wound healing benefit compared to standard care, based on low-strength evidence.

The most commonly evaluated biological agent was platelet-derived growth factor (PDGF), for which there was low-strength evidence of benefit compared to placebo in promoting healing of severe (stage III or IV) ulcers. There was insufficient evidence about the effectiveness of other biological agents.

There was moderate-strength evidence that the most common harms of wound dressings and topical agents were dermatologic complications, including irritation, inflammation, and maceration. However, variability across studies precluded an estimate of adverse events for specific dressings or topical therapies, and evidence was insufficient to determine whether certain types of dressings or topical therapies were more likely to cause these complications than others. Few harms were reported with biological agents, but the evidence about the harms of these agents was insufficient to reach conclusions about adverse event rates. Evidence was insufficient to make conclusions about the effectiveness or harms of local wound applications across different ulcer or patient characteristics, or settings.

Surgical interventions for pressure ulcers identified in studies meeting our inclusion criteria were primarily surgical flaps, most commonly myocutaneous and fasciocutaneous flaps. Studies of surgical interventions were nearly all observational, and most were conducted in single centers. All findings related to the comparative effectiveness and harms of surgical interventions was considered low-strength. These findings included a lower rate of ulcer recurrence with sacral ulcers compared to ischial ulcers; a higher rate of recurrent ulcer among patients with spinal cord injury compared with others; greater wound dehiscence rates with surgeries in which bone is removed as part of the operation; and more adverse events with surgery for ischial compared to sacral or trochanteric ulcers. Surgical flap failures requiring reoperation ranged from 12 to 24 percent.

Adjunctive therapies identified in our review included electrical stimulation, electromagnetic therapy, ultrasound, negative pressure wound therapy, light therapy, and laser therapy. Evidence about other adjunctive therapies – including nonthermic therapy, hydrotherapy, vibration, shock wave, and hyperbaric oxygen – was limited to small, single studies. There was moderate-strength evidence that electrical stimulation improved healing rates, but inconclusive evidence about the effect of electrical stimulation on complete wound healing due to heterogeneous findings across studies. Low-strength evidence indicated that the most common adverse effect of electrical stimulation was local skin irritation; and that harms were more common in frail elderly compared to younger populations. There was also low-strength evidence indicating that electromagnetic therapy, therapeutic ultrasound, and negative pressure wound therapy were similar to sham treatment or standard care in wound healing outcomes; there was insufficient evidence to evaluate the harms of those adjunctive therapies. Light therapy provided benefit in terms of wound area reduction but not in terms of complete wound healing, and was not associated with significant adverse events, based on low-strength evidence. There was low-strength evidence that laser therapy was not associated with significant adverse events, but also that it did not provide wound healing benefit over sham or standard treatment.

Findings in Relationship to What is Already Known

The most current, comprehensive evidence about the effectiveness of pressure ulcer treatments comes from a systematic review by Reddy et al., published in December 2008, that evaluated 103 randomized trials published during or prior to August 2008.[7] The review included

studies evaluating support surfaces, nutritional supplements, wound dressings, biological agents, and adjunctive therapies. Our review included evaluations of those treatment categories and additionally evaluated surgical interventions, included observational studies of pressure ulcer treatments, and assessed treatment harms, in studies published through September 14, 2012.

The findings of this prior systematic review were qualitatively similar to ours, with a few exceptions. In the support surface category, Reddy et al. reported that alternating pressure surfaces and low air-loss beds were not superior to standard, non-powered surfaces. They did not, however, report specifically on air-fluidized beds, and only one of the 5 studies of AF beds included in our review were retrieved in their literature search. Our finding that there was moderate-strength evidence that AF beds were more effective than other surfaces in achieving wound area reduction has not, to our knowledge, been reported in prior reviews.

Reddy et al. reported that overall, nutritional supplements did not provide benefit in terms of ulcer healing, but that protein supplementation may provide benefit. Our findings were similar; we found suggestive evidence that mixed nutritional and protein supplementation may provide wound healing benefit, but this conclusion was supported a low strength of evidence.

Our findings with regard to wound dressings and topical therapies, indicating that there was limited evidence to support the use of certain dressings and topical therapies over others, were similar to the conclusions drawn by Reddy et al. They highlighted a study demonstrating the superiority of alginate dressings to dextranomer paste; we also found dextranomer paste to be inferior to dressing but considered the evidence for this to be low-strength. We did find moderate-strength evidence that radiant heat dressings accelerated the rate of wound area reduction, but we did not find evidence of a benefit of radiant heat dressings in terms of complete wound healing. Similar to Reddy et al., we found a potential benefit, based on low-strength evidence, for platelet-derived growth in promoting healing with stage III and IV ulcers.

Our findings for adjunctive therapies were likewise similar to those of Reddy et al. We found low-strength or insufficient evidence for most adjunctive therapies, limiting the ability to make conclusions about the effectiveness and harms of those treatments. The review by Reddy et al. was also similar to ours in its assessment that the overall quality of the literature evaluating pressure ulcer treatments was poor.

Applicability

The applicability of our findings to real-world clinical settings is supported by several features of the body of literature we reviewed. First, the populations studied included a broad representation of patients with pressure ulcers – elderly patients, general populations of patients with limited mobility, patients with spinal cord injury – cared for in a wide variety of settings, including hospitals, nursing homes, wound care clinics, and at home. Second, the interventions represented most of the therapeutic modalities commonly used in clinical settings. Comparators were also commonly used therapies and often included standard care as defined by local practice patterns.

Other features of the studies we identified, however, limit the applicability of our findings. First, the outcome in many studies was wound size (area, volume, or depth) reduction, as opposed to complete wound healing. Although wound size reduction is a reasonable measure of therapeutic effect, in clinical practice the goal of therapy is almost always complete wound healing, making wound size reduction a surrogate outcome with less clinical significance than complete wound healing. A principal reason for findings of wound size reduction without complete wound healing was the short duration of most trials. Complete healing takes time, and

interventions lasting only a few weeks, as was the case for many if not most of the trials included in our review, are less likely to achieve complete wound healing than interventions carried out for periods long enough for complete healing to occur, as they would be in clinical practice.[a]

Studies of surgery are additionally limited by the fact that most were observational and conducted in one or, at most, a few centers. Because surgical technique and quality is often operator- and/or site-dependent, and because outcomes are influenced by local practices, staffing, and other features of the environment, it is difficult to generalize the findings of studies of surgery included in this review.

Implications for Clinical and Policy Decisionmaking

The limitations in applicability discussed above, as well as the limitations of the evidence base discussed below, make it difficult to draw firm conclusions with implications for clinical and policy decisionmaking. Notably, we generated no findings that were supported by a high strength of evidence, and only a few findings supported by moderate-strength evidence. Most findings were based on low-strength evidence, and for many issues there was insufficient evidence to draw any conclusions.

The finding that air-fluidized beds are superior to others might warrant consideration of greater investment in this technology. However, any decisions about such investments would need to take into account both the fact that the effectiveness of these beds was measured in terms of wound size reduction, rather than complete wound healing, and the cost associated with this technology compared to other surfaces.

Nutritional supplementation may provide benefit in terms of wound healing, though the effects of nutritional supplementation were not dramatic, and it was not clear from the studies in our review whether nutritional supplementation was beneficial to all patients or to those with evidence of nutritional deficiencies. Nutritional support is commonly prescribed for ill or debilitated patients with evidence of malnutrition; whether this affects ulcer healing, and whether patients without evidence of malnutrition might benefit from nutritional supplementation, is not clear.

Decisions about dressings and topical applications are often guided by matching the primary functions of different dressings (e.g., absorbent, hydrating) with the primary considerations for treatment of individual ulcers (e.g., dryness, contamination risk, exudate). Given the wide array of options, comparative effectiveness and harms data has great potential to guide individualized decisionmaking. We found limited evidence, however, to provide such guidance. Overall, we did not find substantial evidence to support certain local wound applications over others. There was evidence to suggest that radiant heat improved the pace of wound healing, but not complete wound healing per se. Some biological agents showed promise for the treatment of severe ulcers, but the evidence was not substantial, and in light of the cost of these agents, more and better evidence is likely needed before they are widely adopted.

Surgery is typically reserved for refractory ulcers unlikely to heal with conservative management. Evidence about surgery is limited to mainly single-center observational studies. While we found some evidence to inform decisions and expectations about which ulcers will fare best with surgical intervention, and which surgeries are likely to produce the lowest complication

[a] Secondly, the treatment of pressure ulcers in clinical practice often involves multiple concurrent therapies such as support surfaces, nutritional supplementation, biologic or topical therapies, and adjunctive interventions. No studies compared one combination of concurrent or sequential therapies to another and no conclusions can be drawn regarding the effectiveness of one compared to another.

rates, the influence of those findings on clinical decisionmaking should be tempered by the low quality of the studies that produced the findings, and the potentially limited generalizability of the findings across sites and surgeons.

Adjunctive therapies include therapies that are variably used in the treatment of pressure ulcers. Our review revealed moderate-strength evidence that electrical stimulation may accelerate healing but did not otherwise produce findings that would support greater use of adjunctive therapies.

Limitations of the Comparative Effectiveness Review Process

The most important potential limitations of the of our review process are that we did not identify important studies whose findings might influence clinical and policy decisionmaking, and potential bias either in the conduct of the identified studies or in our evaluation of evidence from those studies. The two main threats to incomplete identification of evidence are an inadequate literature search, and biased reporting of results such that only selected studies were published and retrievable. To overcome these potential limitations, we conducted a comprehensive, broadly inclusive search that produced 6463 study titles and abstracts. Although we excluded studies published before 1985, we do not believe that important studies of therapies used in current practice were missed; the general consistency of our findings with the systematic review by Reddy et al., which included studies published prior to 1985, provides some assurance that our review was not biased by our time frame selection.

Reporting bias is a concern in any systematic review. We were not able to conduct quantitative analyses to evaluate the possibility of reporting bias for most of our findings, because the heterogeneity across studies in our review generally precluded meaningful comparison of effect sizes. Mitigating against the likelihood of reporting bias in our review, however, is the fact that the majority of studies in our review were small (most fewer than 100 patients, many fewer than 50), and most reported no significant effect of the intervention. Reporting bias typically results in selective publication of larger studies and/or those with positive findings. We also conducted grey literature searches to look for unpublished data and did not find evidence of unreported studies.

We took several measures to guard against the influence of bias in the identified studies, or in our evaluation of those studies. Abstracts were reviewed by at least two team members, including a clinician/senior investigator. Studies were extracted based on prespecified data elements, extraction done by one team member was checked by another, and quality rating of studies was performed by two team members and disagreements adjudicated by consensus. Rating of elements of strength of evidence was discussed and calibrated among team members.

Limitations of the Evidence Base

The main limitation of the evidence base in our review was poor study quality. Most trials did not specify randomization method, did not conceal allocation, and did not mask outcomes assessment. Most studies did use intention-to-treat analyses. Most studies were small, and many were underpowered to detect significant differences. Studies were also highly variable in terms of patient populations, ulcer characteristics (e.g., anatomic site, duration, stage), interventions (even within a given intervention category, e.g., different types of foam dressings), and

comparators (especially variability in implementation of standard, or usual, care), limiting our ability to combine or compare results across studies.

Another major limitation of the evidence base relates to the most common outcome measure, wound size reduction. Comparing changes in the size of PUs poses several measurement issues. For example, reduction in the size of larger and smaller PUs is hard to compare. Healing could involve "bridges" that split a large ulcer into two. Measurement in person or from tracings or photographs can be difficult, especially when measurement and photographic techniques are not standardized across studies.

Finally, a major limitation of studies in our review was the duration of interventions and followup periods. Many pressure ulcers, especially more severe ulcers, may take weeks to months to heal. Many of the studies in our review were implemented over a period that did not necessarily allow for complete ulcer healing and therefore detection of significant differences in ulcer healing across groups.

Research Gaps

The major gaps in research identified by our review relate to the limitations of the evidence base as described above. Future research with larger sample sizes, more rigorous adherence to methodological standards for clinical trials, longer followup periods, and more standardized and clinically meaningful outcome measures is needed to inform clinical practice and policy.

One clinical area identified as high-priority by our Technical Expert Panel, for which we found limited evidence, is hyperbaric oxygen therapy. Although studies, and systematic reviews, have evaluated this treatment in chronic wounds generally, its utility among patients with pressure ulcers has not been evaluated specifically.

Conclusions

We found limited evidence to draw firm conclusions about the best approaches for treating pressure ulcers. This finding is consistent with that of a recent systematic review addressing most of the same treatment categories included in our review.[7] Although we did find evidence from five studies indicating a benefit for air-fluidized beds over other support surfaces, from four studies indicating a benefit of radiant heat dressings over other dressings, and from nine studies indicating a benefit of electrical stimulation, but the benefit observed in all cases was wound size reduction or healing rates, rather than completely healed wounds. The balance of costs and potential harms of those technologies against the benefits observed is unclear.

Choices of wound dressings and topical applications are often guided by product availability, local practice patterns, and individualized decisionmaking based for specific patients and the features of a given pressure ulcer. Our review did not generate findings to guide those choices based on evidence. Studies generally did not provide evidence to support the use of one type of commonly used dressing over another. There was evidence that hydrocolloid and foam dressings performed similarly, but evidence for other dressing types – hydrogels, alginates, transparent films, and silicone dressings – compared with each other or to standard gauze dressings was limited. Similarly, there was low-strength or insufficient evidence to judge the balance of effectiveness and harms for nutritional supplementation, topical therapies, biological agents, surgical interventions, and adjunctive therapies other than electrical stimulation, which appeared to improve healing rates. Advancing pressure ulcer care will require more rigorous study to solidify the evidence base for this important and widely used set of treatments.

Results are summarized below in Table 16.

Table 16. Summary of evidence: Pressure ulcer treatment strategies

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Key Question 1. In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?		
Key Outcomes: Support		
Air-fluidized beds	Moderate	Five studies that involved comparing air-fluidized beds to other surfaces all reported better healing in terms of reduction in PU size or stage on air-fluidized beds.
Alternating pressure (AP) beds	Moderate	There was no evidence of differences in healing reduction in ulcer size across different brands and types of alternating pressure beds (four studies).
Alternating pressure (AP) beds compared with other surfaces	Insufficient	The evidence about the effectiveness of alternating pressure surfaces compared with other types of surfaces was inconclusive with studies producing mixed results (three studies).
Alternating pressure (AP) chair cushions	Insufficient	Two studies of alternating pressure chair cushions were conducted in two very different populations (younger people with spinal cord injury and older hospital patients or nursing home residents) and produced conflicting results, that may be due to differences in the populations (three studies).
Low-Air loss (LAL) beds	Moderate	There was no evidence of differences in outcomes with LAL beds compared with foam surfaces (3 of 4 studies), or with LAL beds compared with LAL overlays.
Other support surfaces	Insufficient	Four studies of surfaces presented as innovative and/or more cost effective involved different experimental surfaces and therefore we could not draw conclusions.
Key Outcomes: Nutrition		
Mixed nutritional supplementation	Low	The study quality was generally low across studies of mixed nutritional supplementation, Studies reported small benefits in the reduction of wound size and reduced healing time, but there was no evidence of benefit in terms of complete wound healing.
Protein or amino acid supplementation	Low	Healing and reduction in ulcer size were similar to slightly better among patients receiving high protein, amino acids or amino acid precursors compared to standard care, placebo or other forms of supplementation.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Specific nutrient supplementation	Insufficient	The evidence about the effectiveness and the results of either vitamin C or zinc supplementation to enhance wound healing is inconclusive. Only two studies evaluated specific nutrient supplementation without overall additional nutritional support. One was a trial of the effect of high and low doses of ascorbic acid (vitamin C) that found no significant difference in wound healing, and the other was an observational study of zinc supplementation.
Key Outcomes: Local Wound Applications		
Hydrocolloid dressings compared with Conventional Care	Low	Wound healing was superior with hydrocolloid compared with gauze dressings (10 studies).
Hydrocolloid compared with foam	Moderate	Wound healing outcomes were similar with hydrocolloid and foam dressings (seven studies, pooled RR 1.10, 95% CI 0.85 to 1.42, I^2=25.4%, p = 0.235).
Comparisons of different wound dressings	Insufficient	Evidence regarding the comparative effectiveness of hydrogel, transparent film, silicone, alginate, and gauze dressings was insufficient to draw conclusions.
Radiant heat compared with other dressings	Moderate	Radiant heat dressings produced more rapid wound healing than other dressings, but there was no evidence of benefit in terms of complete wound healing (pooled RR 1.23, 95% CI 0.70 to 2.14, I^2 = 0.0% p =.916).
Debriding enzymes compared with dressings or other topical therapies	Insufficient	There is insufficient evidence about the effectiveness of collagenase and other debriding enzymes in improving wound healing (five studies).
Dextranomer paste compared to wound dressings	Low	Dextranomer paste is inferior to wound dressings (alginate, hydrogel) in promoting wound area reduction
Topical collagen compared with hydrocolloid dressings or standard care	Low	Wound healing was similar with topical collagen compared with hydrocolloid dressings or standard care.
Topical Phenytoin	Insufficient	Three studies of the effectiveness of topical phenytoin used different comparators and produced inconsistent results.
Platelet-derived growth factor	Low	Platelet-derived growth factor was superior to placebo in the healing of stage III and IV pressure ulcers (three studies, strength of evidence: low).
Biological Agents other than platelet-derived growth factor	Insufficient	There was insufficient evidence about the effectiveness of other biological agents used for the treatment of pressure ulcers.
Key Outcomes: Surgery		
Sacral compared to Ischial pressure ulcers	Low	Sacral pressure ulcers have lower recurrence rates after surgery than ischial pressure ulcers
Key Outcomes: Adjunctive		

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Electrical stimulation	Moderate	Electrical stimulation was beneficial in the rate of healing of stage II, III, and IV pressure ulcers based on one good-quality and eight fair-quality randomized trials.
Electrical stimulation	Insufficient	Evidence about the effect of electrical stimulation on complete wound healing of stage II, III, and IV pressure ulcers was inconclusive, due to heterogeneous results from six randomized trials.
Electromagnetic therapy	Low	There was no evidence of benefit with electromagnetic therapy in wound healing of stage II, III, or IV pressure ulcers in patients based on three randomized trials and one systematic review.
Therapeutic ultrasound	Low	There was no evidence of benefit with ultrasound in terms of complete wound healing based on one systematic review of two randomized trials.
Negative pressure wound therapy	Low	There was no evidence of benefit with negative pressure wound therapy in wound healing over 4 to 6 weeks of therapy based on two randomized trials and one observational study.
Light therapy	Low	There was no evidence of benefit with light therapy in complete wound healing based on two randomized trials.
Light therapy	Low	Light therapy may be beneficial in reducing wound surface area over time compared with standard care or sham light therapy based on five randomized trials.
Laser therapy	Low	There was no evidence of benefit with laser therapy in wound healing based on four randomized trials.
Question 1a: Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?		
Support		
	Insufficient	Most of the studies of support surfaces identified for this review did not include any subgroup analyses.
Nutrition		
	Insufficient	Only 3 of the 15 studies analyzed results by PU characteristics and the impact on the conclusion was inconsistent.
Local Wound Applications		
	Insufficient	Few studies conducted subgroup analyses by ulcer characteristics.
Surgery		
	Insufficient	No studies.
Adjunctive		
	Insufficient	

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Question 1b: Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including but not limited to: age; race/ethnicity; body weight; specific medical comorbidities; and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?		
Key Outcomes: Support		
	Insufficient	Few studies presented any subgroup analyses making it impossible to draw any conclusions about the impact of patient characteristics on the effectiveness of different support surfaces in PU healing.
Key Outcomes: Nutrition		
	Insufficient	No studies
Key Outcomes: Local Wound Applications		
	Insufficient	Indirect comparisons across studies to evaluate the possibility that treatment effectiveness is modified by ulcer or patient characteristics are limited by the fact that there were relatively few studies evaluating any given treatment comparison and by the fact that aside from ulcer stage and location, patient age and gender, few variables were reported consistently across studies.
Key Outcomes: Surgery		
	Low	Spinal cord injured patients appeared to be at greater risk of recurrent pressure ulcer after surgical flap than other patients with pressure ulcers.
Key Outcomes: Adjunctive		
Electromagnetic therapy *Therapeutic ultrasound* *Negative pressure wound therapy* *Light therapy* *Laser therapy*	Insufficient	Insufficient evidence to determine if the effectiveness of electromagnetic therapy compared with sham EMT; ultrasound therapy compared with sham US; negative pressure wound therapy; light therapy; or laser therapy varied based on features of the pressure ulcers, characteristics of the patient.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Question 1c: Does the comparative effectiveness of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?		
Key Outcomes: Support		
	Insufficient	Few studies presented any subgroup analyses making it impossible to draw any conclusions about the impact of patient care settings on the effectiveness of different support surfaces in PU healing.
Key Outcomes: Nutrition		
	Insufficient	No studies
Key Outcomes: Local Wound Applications		
	Insufficient	Indirect comparisons across studies to evaluate the possibility that treatment effectiveness is modified by patient care setting characteristics are limited by the fact that there were relatively few studies evaluating any given treatment comparison by study setting, and that few variables were reported consistently across studies.
Surgery		
	Insufficient	No studies.
Key Outcomes: Adjunctive		
Electromagnetic therapy *Therapeutic ultrasound* *Negative pressure wound therapy* *Light therapy* *Laser therapy*	Insufficient	Insufficient evidence to determine if the effectiveness of electromagnetic therapy compared with sham EMT; ultrasound therapy compared with sham US; negative pressure wound therapy; light therapy; or laser therapy varied based on features of the patient care settings.
Question 2: What are the harms of treatments for pressure ulcers?		
Harms: Support		
	Insufficient	Few of the identified studies (7 out of 22) explicitly addressed harms attributable to support surfaces. In those where harms are mentioned, most reported no significant differences in harms across the different support surfaces.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Harms: Nutrition		
	Insufficient	Harms or adverse events were reported in about half of the studies (8 of 15), but they reported different harms, did not allow describe the harm, or did not specify if it was related to treatment.
Harms: Local Wound Applications		
Dressings and topical therapies	Moderate	Harms reported with dressings and topical therapies for pressure ulcers most commonly included skin irritation and inflammation and tissue damage and maceration. Variability in study populations, interventions, adverse event measurement, and reporting precluded an estimate of adverse event rates for dressings and topical therapies.
Dressings and topical therapies	Insufficient	There was insufficient evidence as to whether specific dressing types or topical therapies are associated with fewer harms than others (seven studies).
Biologic agents	Insufficient	Few harms were reported with biological agents. There was insufficient evidence about differences in the effectiveness or harms of wound dressings, topical treatments, or biological agents according to ulcer, patient, or setting characteristics.
Harms: Surgery		
	Low	Reoperation due to recurrence or flap failure ranged from 12 to 24 percent.
Harms: Adjunctive		
Electrical stimulation	Low	The most common adverse effect of electrical stimulation was local skin irritation.
Electromagnetic therapy *Therapeutic ultrasound* *Negative pressure wound therapy*	Insufficient	There is insufficient evidence about the harms of electromagnetic therapy, ultrasound, and negative pressure wound therapy
Light therapy	Low	Light therapy was not associated with significant adverse events based on four randomized studies
Laser therapy	Low	Short-term use of laser therapy was not associated with significant adverse events or overall withdrawal based on three randomized studies
Question 2a: Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?		
Harms: Support		
	Insufficient	No studies
Harms: Nutrition		
	Insufficient	No studies
Harms: Local Wound Applications		
	Insufficient	No studies reported subgroup analyses to evaluate harms by ulcer, patient, or setting characteristics.

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Harms: Surgery		
	Low	Wound dehiscence is more common if bone is removed at time of surgical procedure.
	Low	Ischial sites are associated with greater complications than sacral or trochanteric sites
Harms: Adjunctive		
	Insufficient	There was insufficient evidence to determine if differences in harms of any adjunctive therapies exist based on features of the pressure ulcers
Question 2b: Do the harms of treatment strategies differ according to patient characteristics, including: age, race/ethnicity; body weight; specific medical comorbidities; and knows risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?		
Harms: Support		
	Insufficient	No studies
Harms: Nutrition		
	Insufficient	No studies
Harms: Local Wound Applications		
	Insufficient	No studies
Harms: Surgery		
	Insufficient	No studies
Harms: Adjunctive		
Electrical stimulation	Low	Frail elderly patients experience more adverse events with electrical stimulation compared with a younger population.
Question 2c: Do the harms of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including but not limited to nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?		
Harms: Support		
	Insufficient	No studies
Harms: Nutrition		
	Insufficient	No studies

Key Question/Treatment Strategy	Strength of Evidence	Conclusion
Harms: Local Wound Applications		
	Insufficient	No studies
Harms: Surgery		
	Insufficient	No studies
Harms: Adjunctive		
	Insufficient	There was insufficient evidence to determine if differences existed in harms based on patient care setting or features of the patient care setting.

Note: PU, pressure ulcer.

Funding Source: Agency for Healthcare Research and Quality

References

1. Bergstrom N, Bennett MA, Carlson CE, et al. Pressure Ulcer Treatment. Clin Pract Guidel Quick Ref Guide Clin. 1994;15.

2. Graves N, Birrell F, Whitby M. Effect of pressure ulcers on length of hospital stay. Infect Control Hosp Epidemiol. 2005;26(3):293-7.

3. Lyder CH. Pressure ulcer prevention and management. JAMA. 2003 Jan 8;289(2):223-6. PMID: 12517234.

4. NPUAP. Pressure Ulcer Prevention and Treatment: Clinical Practice guidline. National Pressure Ulcer Advisory Panel and European Pressure Ulcer Advisory Panel. 2009.

5. AHRQ. Methods Guide for Effectiveness and Comparative Effectiveness Reviews: Agency for Healthcare Research & Quality; 2011.

6. Institute of Medicine. Finding What Works in Health Care: Standards for Systematic Reviews. Washington, DC: The National Academy of Sciences; 2011.

7. Reddy M, Gill SS, Kalkar SR, et al. Treatment of pressure ulcers: a systematic review. JAMA. 2008 Dec 10;300(22):2647-62. PMID: 19066385.

8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. JECH. 1998;52(6):377-84. PMID: 9764259.

9. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35. PMID: 11306229.

10. USPSTF. U.S. Preventive Services Task Force Procedures Manual: United States PreventiveServices Task Force; 2008.

11. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58. PMID: 12111919.

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.

13. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2011;64(11):1198-207. PMID: 21463926.

14. NPUAP. Support Surfaces Standards Initiative - Terms and Definitions Related to Support Surfaces. In: Panel NPUA, editor. Ver. 01/29/2007 ed: National Pressure Ulcer Advisory Panel; 2007. p. 10.

15. Russell L, Reynolds TM, Carr J, et al. Randomised controlled trial of two pressure-relieving systems. J Wound Care. 2000(a) Feb;9(2):52-5. PMID: 11933280.

16. Russell L, Reynolds T, Carr J, et al. A comparison of healing rates on two pressure-relieving systems. Br J Nurs. 2000(b) Dec 8-2001 Jan 10;9(22):2270-80. PMID: 12271193.

17. Evans D, Land L, Geary A. A clinical evaluation of the Nimbus 3 alternating pressure mattress replacement system. J Wound Care. 2000 Apr;9(4):181-6. PMID: 11933303.

18. Land L, Evans D, Geary A, et al. A clinical evaluation of an alternating-pressure mattress replacement system in hospital and residential care settings. J Tissue Viability. 2000 Jan;10(1):6-11. PMID: 10839090.

19. Izutsu T, Matsui T, Satoh T, et al. Effect of rolling bed on decubitus in bedridden nursing home patients. Tohoku J Exp Med. 1998 Feb;184(2):153-7. PMID: 9605022.

20. Ochs RF, Horn SD, van Rijswijk L, et al. Comparison of air-fluidized therapy with other support surfaces used to treat pressure ulcers in nursing home residents. Ostomy Wound Manage. 2005 Feb;51(2):38-68. PMID: 15699554.

21. Day A, Leonard F. Seeking quality care for patients with pressure ulcers. Decubitus; 1993. p. 32-43.

22. Ferrell BA, Osterweil D, Christenson P. A randomized trial of low-air-loss beds for treatment of pressure ulcers. JAMA. 1993;269(4):494-7. PMID: 8338511.

23. Branom R, Rappl LM. "Constant force technology" versus low-air-loss therapy in the treatment of pressure ulcers.[Erratum appears in Ostomy Wound Manage 2001 Nov;47(11):6]. Ostomy Wound Manage. 2001 Sep;47(9):38-46. PMID: 11889743.

24. Allman RM, Walker JM, Hart MK, et al. Air-fluidized beds or conventional therapy for pressure sores. A randomized trial. Ann Intern Med. 1987 Nov;107(5):641-8. PMID: 3310792.

25. Jackson BS, Chagares R, Nee N, et al. The effects of a therapeutic bed on pressure ulcers: an experimental study. J Enterostomal Ther. 1988 Nov-Dec;15(6):220-6. PMID: 3204209.

26. Makhsous M, Lin F, Knaus E, et al. Promote pressure ulcer healing in individuals with spinal cord injury using an individualized cyclic pressure-relief protocol. Adv Skin Wound Care. 2009 Nov;22(11):514-21. PMID: 20026933.

27. Strauss MJ, Gong J, Gary BD, et al. The cost of home air-fluidized therapy for pressure sores. A randomized controlled trial. J Fam Pract. 1991 Jul;33(1):52-9. PMID: 2056290.

28. Rosenthal MJ, Felton RM, Nastasi AE, et al. Healing of advanced pressure ulcers by a generic total contact seat: 2 randomized comparisons with low air loss bed treatments. Arch Phys Med Rehabil. 2003 Dec;84(12):1733-42. PMID: 14669176.

29. Munro BH, Brown L, Heitman BB. Pressure ulcers: one bed or another? Geriatr Nurs. 1989;10(4):190-2. PMID: 2777121.

30. Caley. randomized prospective trial of two types of low-air-loss therapy, caley. Clinical Symposium on Pressure Ulcer and Wound Management. 1994:1-2.

31. Mulder G, Taro N, Seeley J, et al. A study of pressure ulcer response to low air loss beds vs. conventional treatment. J Geriatr Dermatol. 1994;2(3):87-91.

32. Devine B. Alternating pressure air mattresses in the management of established pressure sores. J Tissue Viability. 1995;5(3):94-8.

33. Nixon J, Nelson EA, Cranny G, et al. Pressure relieving support surfaces: a randomised evaluation. Health Technol Assess. 2006 Jul;10(22):iii-iv, ix-x, 1-163. PMID: 16750060.

34. Russell L, Reynolds TM, Towns A, et al. Randomized comparison trial of the RIK and the Nimbus 3 mattresses. Br J Nurs. 2003(a) Feb 27-Mar 12;12(4):254, 6-9. PMID: 12671572.

35. Keogh A, Dealey C. Profiling beds versus standard hospital beds: effects on pressure ulcer incidence outcomes. J Wound Care. 2001 Feb;10(2):15-9. PMID: 12964222.

36. . A randomised controlled trial comparing the healing of pressure sores upon two pressure-redistributing seat cushions. Proceedings of the 7th European European Conferences on Advances in Wound Management 18-20 November; 1997; Harrogate, UK.

37. Groen HW, Groenier KH, Schuling J. Comparative study of a foam mattress and a water mattress. J Wound Care. 1999 Jul;8(7):333-5. PMID: 10776222.

38. Malbrain M, Hendriks B, Wijnands P, et al. A pilot randomised controlled trial comparing reactive air and active alternating pressure mattresses in the prevention and treatment of pressure ulcers among medical ICU patients. J Tissue Viability; 2010. p. 7-15.

39. Thompson P, Anderson J, Langemo D, et al. Support Surfaces: Definitions and Utilization for Patient Care. Adv Skin Wound Care. 2008;21(6):264-6. PMID: 18525248

40. McInnes E, National Institite for Clinical E. The use of pressure-relieving devices (beds, mattresses and overlays) for the prevention of pressure ulcers in primary and secondary care. J Tissue Viability. 2004 Jan;14(1):4-6, 8, 10 passim. PMID: 14768130.

41. McInnes E, Jammali-Blasi A, Bell-Syer SE, et al. Support surfaces for pressure ulcer prevention. Cochrane Database Syst Rev. 2011;4:CD001735. PMID: 21491384.

42. Phipps M, Bauman B, Berner D, et al. Staging care for pressure sores. Am J Nurs. 1984;84(8):999-1003. PMID: 6565467

43. European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel. Prevention and treatment of pressure ulcers: quick reference guide. Washington, DC: National Pressure Ulcer Advisory Panel; 2009.

44. Benati G, Delvecchio S, Cilla D, et al. Impact on pressure ulcer healing of an arginine-enriched nutritional solution in patients with severe cognitive impairment. Arch Gerontol Geriatr Suppl. 2001;7:43-7. PMID: 11431045.

45. Cereda E, Gini A, Pedrolli C, et al. Disease-specific, versus standard, nutritional support for the treatment of pressure ulcers in institutionalized older adults: a randomized controlled trial. J Am Geriatr Soc. 2009 Aug;57(8):1395-402. PMID: 19563522.

46. Desneves KJ, Todorovic BE, Cassar A, et al. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: a randomised controlled trial. Clin Nutr. 2005 Dec;24(6):979-87. PMID: 16297506.

47. Lee SK, Posthauer ME, Dorner B, et al. Pressure ulcer healing with a concentrated, fortified, collagen protein hydrolysate supplement: a randomized controlled trial. Adv Skin Wound Care. 2006 Mar;19(2):92-6. PMID: 16557055.

48. Meaume S, Kerihuel JC, Constans T, et al. Efficacy and safety of ornithine alpha-ketoglutarate in heel pressure ulcers in elderly patients: results of a randomized controlled trial. J Nutr Health Aging. 2009 Aug;13(7):623-30. PMID: 19621198.

49. Myers SA, Takiguchi S, Slavish S, et al. Consistent wound care and nutritional support in treatment. Decubitus. 1990 Aug;3(3):16-28. PMID: 2119183.

50. Ohura T, Nakajo T, Okada S, et al. Evaluation of effects of nutrition intervention on healing of pressure ulcers and nutritional states (randomized controlled trial). Wound Repair Regen. 2011 May-Jun;19(3):330-6. PMID: 21539650.

51. Ter Riet G, Kessels AGH, Knipschild PG. Randomized clinical trial of ascorbic acid in the treatment of pressure ulcers. J Clin Epidemiol. 1995;48(12):1453-60. PMID: 8543959.

52. Van Anholt RD, Sobotka L, Meijer EP, et al. An arginine- and micronutrient-enriched nutritional supplement accelerates pressure ulcer healing and reduces wound care in non-malnourished patients. EWMA Journal; 2010. p. 45.

53. Barnes P, Jr., Sauter TE, Zaheri S. Subnormal prealbumin levels and wound healing. Tex Med. 2007 Aug;103(8):65-8. PMID: 19113064.

54. Breslow RA, Hallfrisch J, Guy DG, et al. The importance of dietary protein in healing pressure ulcers. J Am Geriatr Soc. 1993;41(4):357-62. PMID: 8463519.

55. Brewer S, Desneves K, Pearce L, et al. Effect of an arginine-containing nutritional supplement on pressure ulcer healing in community spinal patients. J Wound Care. 2010 Jul;19(7):311-6. PMID: 20616774.

56. Houston S, Haggard J, Williford J, Jr., et al. Adverse effects of large-dose zinc supplementation in an institutionalized older population with pressure ulcers [4]. J Am Geriatr Soc. 2001;49(8):1130-2. PMID: 11555083.

57. Frias Soriano L, Lage Vazquez MA, Maristany CP-P, et al. The effectiveness of oral nutritional supplementation in the healing of pressure ulcers. J Wound Care. 2004 Sep;13(8):319-22. PMID: 15469215.

58. Yamamoto T, Fujioka M, Kitamura R, et al. Evaluation of nutrition in the healing of pressure ulcers: are the EPUAP nutritional guidelines sufficient to heal wounds European Pressure Ulcer Advisory Panel. Wounds. 2009;21(6):153-7.

59. Chernoff R. Policy: nutrition standards for treatment of pressure ulcers. Nutr Rev. 1996 Jan;54(1 Pt 2):S43-4. PMID: 8919679.

60. Henderson CT, Trumbore LS, Mobarhan S, et al. Prolonged tube feeding in long-term care: nutritional status and clinical outcomes. J Am Coll Nutr. 1992;11(3):309-25. PMID: 1619183.

61. Taylor TV, Rimmer S, Day B, et al. Ascorbic acid supplementation in the treatment of pressure-sores. Lancet. 1974;2(7880):544-6. PMID: 4140267.

62. Hollisaz MT, Khedmat H, Yari F. A randomized clinical trial comparing hydrocolloid, phenytoin and simple dressings for the treatment of pressure ulcers [ISRCTN33429693]. BMC Dermatol. 2004;4(1):18. PMID: 15601464.

63. Alm A, Hornmark AM, Fall PA, et al. Care of pressure sores: a controlled study of the use of a hydrocolloid dressing compared with wet saline gauze compresses. Acta Derm Venereol Suppl (Stockh). 1989;149:1-10. PMID: 2694713.

64. Xakellis. Hydrocolloid versus saline-gauze dressings in treating pressure ulcers: a cost-effectiveness analysis. Arch Phys Med Rehabil. 1992;73:463-9. PMID: 1580775.

65. Chang KW, Alsagoff S, Ong KT, et al. Pressure ulcers--randomised controlled trial comparing hydrocolloid and saline gauze dressings. Med J Malaysia. 1998 Dec;53(4):428-31. PMID: 10971989.

66. Colwell JC, Foreman MD, Trotter JP. A comparison of the efficacy and cost-effectiveness of two methods of managing pressure ulcers. Decubitus. 1993 Jul;6(4):28-36. PMID: 8297488.

67. Gorse GJ, Messner RL. Improved pressure sore healing with hydrocolloid dressings. Arch Dermatol. 1987 Jun;123(6):766-71. PMID: 3555355.

68. Kim YC, Shin JC, Park CI, et al. Efficacy of hydrocolloid occlusive dressing technique in decubitus ulcer treatment: a comparative study. Yonsei Med J. 1996 Jun;37(3):181-5. PMID: 8826783.

69. Mulder GD, Altman M, Seeley JE, et al. Prospective randomized study of the efficacy of hydrogel, hydrocolloid, and saline solution -- moistened dressings on the management of pressure ulcers. Wound Repair Regen. 1993;1(4):213-8. PMID: 17166097.

70. Neill K, Conforti C, Kedas A, et al. Pressure Sore Response to a New Hydrocolloid Dressing. Wounds. 1989;1:173-85.

71. Winter A, Hewitt H. Testing a hydrocolloid. Nurs Times. 1990 Dec 12-8;86(50):59-62. PMID: 2255648.

72. Matzen S, Peschardt A, Alsbjorn B. A new amorphous hydrocolloid for the treatment of pressure sores: a randomised controlled study. Scand J Plast Reconstr Surg Hand Surg. 1999 Mar;33(1):13-5. PMID: 10207960.

73. Kaya AZ, Turani N, Akyuz M. The effectiveness of a hydrogel dressing compared with standard management of pressure ulcers. J Wound Care. 2005 Jan;14(1):42-4. PMID: 15656468.

74. Thomas DR, Goode PS, LaMaster K, et al. Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomized, controlled trial. Adv Wound Care. 1998 Oct;11(6):273-6. PMID: 10326343.

75. Yastrub DJ. Relationship between type of treatment and degree of wound healing among institutionalized geriatric patients with stage II pressure ulcers... reprinted with permission from the author and Nurse Practitioner Associates for Continuing Education. Care Manag J. 2004;5(4):213-8.

76. Payne WG, Posnett J, Alvarez O, et al. A prospective, randomized clinical trial to assess the cost-effectiveness of a modern foam dressing versus a traditional saline gauze dressing in the treatment of stage II pressure ulcers. Ostomy Wound Manage. 2009 Feb;55(2):50-5. PMID: 19246785.

77. Kraft MR, Lawson L, Pohlmann B, et al. A comparison of Epi-Lock and saline dressings in the treatment of pressure ulcers. Decubitus. 1993 Nov;6(6):42-4, 6, 8. PMID: 8286026.

78. Sebern MD. Pressure ulcer management in home health care: efficacy and cost effectiveness of moisture vapor permeable dressing. Arch Phys Med Rehabil. 1986 Oct;67(10):726-9. PMID: 3533007.

79. Kurzuk-Howard G, Simpson L, Palmieri A. Decubitus ulcer care: a comparative study. West J Nurs Res. 1985 Feb;7(1):58-79. PMID: 3850687.

80. Oleske DM, Smith XP, White P, et al. A randomized clinical trial of two dressing methods for the treatment of low-grade pressure ulcers. J Enterostomal Ther. 1986 May-Jun;13(3):90-8. PMID: 3519718.

81. Parnell LKS, Ciufi B, Gokoo CF. Preliminary use of a hydrogel containing enzymes in the treatment of stage II and stage III pressure ulcers. Ostomy Wound Manage. 2005 Aug;51(8):50-60. PMID: 16234576.

82. Day A, Dombranski S, Farkas C, et al. Managing sacral pressure ulcers with hydrocolloid dressings: results of a controlled, clinical study. Ostomy Wound Manage. 1995 Mar;41(2):52-4, 6, 8 passim. PMID: 7598778.

83. Darkovich SL, Brown-Etris M, Spencer M. Biofilm hydrogel dressing: a clinical evaluation in the treatment of pressure sores. Ostomy Wound Manage. 1990 Jul-Aug;29:47-60. PMID: 2202317.

84. Motta G, Dunham L, Dye T, et al. Clinical efficacy and cost-effectiveness of a new synthetic polymer sheet wound dressing. Ostomy Wound Manage. 1999 Oct;45(10):41, 4-6, 8-9. PMID: 10687651.

85. Brown-Etris M, Milne C, Orsted H, et al. A prospective, randomized, multisite clinical evaluation of a transparent absorbent acrylic dressing and a hydrocolloid dressing in the management of Stage II and shallow Stage III pressure ulcers. Adv Skin Wound Care. 2008 Apr;21(4):169-74. PMID: 18385577.

86. Banks V, Bale S, Harding K. The use of two dressings for moderately exuding pressure sores. J Wound Care. 1994(b);3(3):132-4.

87. Honde C, Derks C, Tudor D. Local treatment of pressure sores in the elderly: amino acid copolymer membrane versus hydrocolloid dressing. J Am Geriatr Soc. 1994 Nov;42(11):1180-3. PMID: 7525682.

88. Seeley J, Jensen JL, Hutcherson J. A randomized clinical study comparing a hydrocellular dressing to a hydrocolloid dressing in the management of pressure ulcers. Ostomy Wound Manage. 1999 Jun;45(6):39-44, 6-7. PMID: 10655861.

89. Banks V, Bale SE, Harding KG. Comparing two dressings for exuding pressure sores in community patients. J Wound Care. 1994(a);3(4):175-8.

90. Brod M, McHenry E, Plasse TF, et al. A randomized comparison of poly-hema and hydrocolloid dressings for treatment of pressure sores. Arch Dermatol. 1990 Jul;126(7):969-70. PMID: 2193631.

91. Bale S, Hagelstein S, Banks V, et al. Costs of dressings in the community. J Wound Care. 1998 Jul;7(7):327-30. PMID: 9791356.

92. Thomas S, Banks V, Bale S, et al. A comparison of two dressings in the management of chronic wounds. J Wound Care. 1997 Sep;6(8):383-6. PMID: 9341430.

93. Belmin J, Meaume S, Rabus M-T, et al. Sequential treatment with calcium alginate dressings and hydrocolloid dressings accelerates pressure ulcer healing in older subjects: a multicenter randomized trial of sequential versus nonsequential treatment with hydrocolloid dressings alone. J Am Geriatr Soc. 2002 Feb;50(2):269-74. PMID: 12028208.

94. Meaume S, Vallet D, Morere MN, et al. Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection.[Erratum appears in J Wound Care. 2005 Nov;14(10):479]. J Wound Care. 2005 Oct;14(9):411-9. PMID: 16240620.

95. Meaume S, Van De Looverbosch D, Heyman H, et al. A study to compare a new self-adherent soft silicone dressing with a self-adherent polymer dressing in stage II pressure ulcers. Ostomy Wound Manage. 2003 Sep;49(9):44-51. PMID: 14581709.

96. Viamontes L, Temple D, Wytall D, et al. An evaluation of an adhesive hydrocellular foam dressing and a self-adherent soft silicone foam dressing in a nursing home setting. Ostomy Wound Manage. 2003 Aug;49(8):48-52, 4-6, 8. PMID: 14631663.

97. Thomas DR, Diebold MR, Eggemeyer LM. A controlled, randomized, comparative study of a radiant heat bandage on the healing of stage 3-4 pressure ulcers: a pilot study. J Am Med Dir Assoc. 2005 Jan-Feb;6(1):46-9. PMID: 15871870.

98. Price P, Bale S, Crook H, et al. The effect of a radiant heat dressing on pressure ulcers. J Wound Care. 2000 Apr;9(4):201-5. PMID: 11933306.

99. Kloth LC, Berman JE, Nett M, et al. A randomized controlled clinical trial to evaluate the effects of noncontact normothermic wound therapy on chronic full-thickness pressure ulcers. Adv Skin Wound Care. 2002 Nov-Dec;15(6):270-6. PMID: 12477979.

100. Whitney JD, Salvadalena G, Higa L, et al. Treatment of pressure ulcers with noncontact normothermic wound therapy: healing and warming effects. J Wound Ostomy Continence Nurs. 2001 Sep;28(5):244-52. PMID: 11557928.

101. Kerihuel JC. Effect of activated charcoal dressings on healing outcomes of chronic wounds. J Wound Care. 2010 May;19(5):208, 10-2, 14-5. PMID: 20505594.

102. Small N, Mulder M, Mackenzie MJ, et al. A comparative analysis of pressure sore treatment modalities in community settings. Curationis. 2002 Feb;25(1):74-82. PMID: 12096575.

103. Yapucu Gunes U, Eser I. Effectiveness of a honey dressing for healing pressure ulcers. J Wound Ostomy Continence Nurs. 2007 Mar-Apr;34(2):184-90. PMID: 17413836.

104. Burgos A, Gimenez J, Moreno E, et al. Collagenase ointment application at 24- versus 48-hour intervals in the treatment of pressure ulcers. A randomised multicentre study. Clin Drug Investig. 2000;19(6):399-407.

105. Burgos A, Gimenez J, Moreno E, et al. Cost, efficacy, efficiency and tolerability of collagenase ointment versus hydrocolloid occlusive dressing in the treatment of pressure ulcers. A comparative, randomised, multicentre study. Clin Drug Investig. 2000;19(5):357-65.

106. Alvarez OM, Fernandez-Obregon A, Rogers RS, et al. Chemical debridement of pressure ulcers: a prospective, randomized, comparative trial of collagenase and papain/urea formulations. Wounds. 2000;12(2):15-25.

107. Muller E, van Leen MW, Bergemann R. Economic evaluation of collagenase-containing ointment and hydrocolloid dressing in the treatment of pressure ulcers. Pharmacoeconomics. 2001;19(12):1209-16. PMID: 11772156.

108. Agren MS, Stromberg HE. Topical treatment of pressure ulcers. A randomized comparative trial of Varidase and zinc oxide. Scand J Plast Reconstr Surg. 1985;19(1):97-100. PMID: 3895409.

109. Rhodes RS, Heyneman CA, Culbertson VL, et al. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. Ann Pharmacother. 2001 Jun;35(6):675-81. PMID: 11408983.

110. Subbanna PK, Margaret Shanti FX, George J, et al. Topical phenytoin solution for treating pressure ulcers: a prospective, randomized, double-blind clinical trial. Spinal Cord. 2007 Nov;45(11):739-43. PMID: 17279096.

111. Sayag J, Meaume S, Bohbot S. Healing properties of calcium alginate dressings. J Wound Care. 1996 Sep;5(8):357-62. PMID: 8954425.

112. Colin D, Kurring PA, Yvon C. Managing sloughy pressure sores. J Wound Care. 1996 Nov;5(10):444-6. PMID: 9117814.

113. Graumlich JF, Blough LS, McLaughlin RG, et al. Healing pressure ulcers with collagen or hydrocolloid: A randomized, controlled trial. J Am Geriatr Soc. 2003;51(2):147-54. PMID: 12558709.

114. Zeron HM, Krotzsch Gomez FE, Munoz REH. Pressure ulcers: a pilot study for treatment with collagen polyvinylpyrrolidone. Int J Dermatol. 2007 Mar;46(3):314-7. PMID: 17343594.

115. Nisi G, Brandi C, Grimaldi L, et al. Use of a protease-modulating matrix in the treatment of pressure sores. Chir Ital. 2005 Jul-Aug;57(4):465-8. PMID: 16060184.

116. Gerding GA, Browning JS. Oxyquinoline-containing ointment vs. standard therapy for stage I and stage II skin lesions. Dermatol Nurs. 1992 Oct;4(5):389-98. PMID: 1482629.

117. Chuangsuwanich A, Charnsanti O, Lohsiriwat V, et al. The efficacy of silver mesh dressing compared with silver sulfadiazine cream for the treatment of pressure ulcers. J Med Assoc Thai. 2011 May;94(5):559-65. PMID: 21675444.

118. Sipponen A, Jokinen JJ, Sipponen P, et al. Beneficial effect of resin salve in treatment of severe pressure ulcers: a prospective, randomized and controlled multicentre trial. Br J Dermatol. 2008 May;158(5):1055-62. PMID: 18284391.

119. Guthrie M, Diakiw J, Zaydon AC, et al. A randomized double-blind clinical study of dermagran dual therapeutic system in the treatment of decubitus ulcers. Wounds. 1989;1(3):142-54.

120. Kuflik A, Stillo JV, Sanders D, et al. Petrolatum versus Resurfix ointment in the treatment of pressure ulcers. Ostomy Wound Manage. 2001 Feb;47(2):52-6. PMID: 11235499.

121. LeVasseur SA, Helme RD. A double-blind clinical trial to compare the efficacy of an active based cream F14001 against a placebo non-active based cream for the treatment of pressure ulcers in a population of elderly subjects. J Adv Nurs. 1991 Aug;16(8):952-6. PMID: 1779084.

122. Shamimi Nouri K, Karimian R, Nasli E, et al. Topical application of Semelil (ANGIPARS(trademark)) in treatment of pressure ulcers: A randomized clinical trial. Daru. 2008;16(SUPPL. 1):54-7.

123. Hsu YC, Chang HH, Chen MF, et al. Therapeutic effect of sheng-ji-san on pressure ulcers. Am J Chin Med. 2000;28(3-4):391-9. PMID: 11154053.

124. Felzani G, Spoletini I, Convento A, et al. Effect of lysine hyaluronate on the healing of decubitus ulcers in rehabilitation patients. Adv Ther. 2011 May;28(5):439-45. PMID: 21499725.

125. Tytgat H, Van Asch H. Topical ketanserin in the treatment of decubitus ulcers: A double-blind study with 2% ketanserin ointment against placebo. Adv Ther. 1988;5(4):143-52.

126. Narayanan S, Van Vleet J, Strunk B, et al. Comparison of pressure ulcer treatments in long-term care facilities: clinical outcomes and impact on cost. J Wound Ostomy Continence Nurs. 2005 May-Jun;32(3):163-70. PMID: 15931146.

127. Burgos A, Gimenez J, Moreno E, et al. Cost, efficacy, efficency and tolerability of collagenase ointment versus hydrocolloid occlusive dressing in the treatment of pressure ulcers. Clin Drug Investig. 2000;19(5):357-65.

128. Pullen R, Popp R, Volkers P, et al. Prospective randomized double-blind study of the wound-debriding effects of collagenase and fibrinolysin/deoxyribonuclease in pressure ulcers. Age Ageing. 2002 Mar;31(2):126-30. PMID: 11937475.

129. Hindryckx P, De Cuyper C, Hendrickx B, et al. The treatment of infected decubitus ulcers with 1% silver sulfadiazine cream. Curr Ther Res Clin Exp. 1990;48(3):535-9.

130. Rees RS, Robson MC, Smiell JM, et al. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study. Wound Repair Regen. 1999 May-Jun;7(3):141-7. PMID: 10417749.

131. Robson MC, Phillips LG, Thomason A, et al. Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. Lancet. 1992 Jan 4;339(8784):23-5. PMID: 1345953.

132. Robson MC, Phillips LG, Lawrence WT, et al. The safety and effect of topically applied recombinant basic fibroblast growth factor on the healing of chronic pressure sores. Ann Surg. 1992 Oct;216(4):401-6; discussion 6-8. PMID: 1417189.

133. Mustoe TA, Cutler NR, Allman RM, et al. A phase II study to evaluate recombinant platelet-derived growth factor-BB in the treatment of stage 3 and 4 pressure ulcers. Arch Surg. 1994 Feb;129(2):213-9. PMID: 8304833.

134. Scevola S, Nicoletti G, Brenta F, et al. Allogenic platelet gel in the treatment of pressure sores: a pilot study. Int Wound J. 2010 Jun;7(3):184-90. PMID: 20455960.

135. Landi F, Aloe L, Russo A, et al. Topical treatment of pressure ulcers with nerve growth factor: a randomized clinical trial. Ann Intern Med. 2003 Oct 21;139(8):635-41. PMID: 14568851.

136. Payne WG, Wright TE, Ochs D, et al. An exploratory study of dermal replacement therapy in the treatment of stage III pressure ulcers. J Appl Res. 2004;4(1):12-23.

137. Hirshberg J, Coleman J, Marchant B, et al. TGF-beta3 in the treatment of pressure ulcers: a preliminary report. Adv Skin Wound Care. 2001 Mar-Apr;14(2):91-5. PMID: 11899912.

138. Robson MC, Hill DP, Smith PD, et al. Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. Ann Surg. 2000 Apr;231(4):600-11. PMID: 10749622.

139. Zuloff-Shani A, Adunsky A, Even-Zahav A, et al. Hard to heal pressure ulcers (stage III-IV): efficacy of injected activated macrophage suspension (AMS) as compared with standard of care (SOC) treatment controlled trial. Arch Gerontol Geriatr. 2010 Nov-Dec;51(3):268-72. PMID: 20034682.

140. Danon D, Madjar J, Edinov E, et al. Treatment of human ulcers by application of macrophages prepared from a blood unit. Exp Gerontol. 1997 Nov-Dec;32(6):633-41. PMID: 9785089.

141. Robson MC, Phillips LG, Thomason A, et al. Recombinant human platelet-derived growth factor-BB for the treatment of chronic pressure ulcers. Ann Plast Surg. 1992;29(3):193-201. PMID: 1524367.

142. Payne WG, Ochs DE, Meltzer DD, et al. Long-term outcome study of growth factor-treated pressure ulcers. Am J Surg. 2001 Jan;181(1):81-6. PMID: 11248182.

143. Whitney J, Higa L, Savadalena G, et al. Effect of radiant heat treatment on pressure ulcer healing: preliminary findings. 31st Annual Wound, Ostomy and Continence Conference. 1999.

144. Meaume S, Ourabah Z, Charru P, et al. Optimizing wound care with a new lipido-colloid dressing (Urgotul Duo). Br J Nurs. 2007 Mar 22-Apr 11;16(6):S4, S6, S8 passim. PMID: 17505400.

145. Stoker FM. A major contributor. Evaluation of Comfeel Pressure Relieving Dressing. Prof Nurse. 1990 Sep;5(12):644-53. PMID: 2217219.

146. Moody M. Calcium alginate: a dressing trial. Nurs Stand. 1991;5(50):3-6. PMID: 1911033.

147. Sorensen JL, Jorgensen B, Gottrup F. Surgical treatment of pressure ulcers. Am J Surg. 2004 Jul;188(1A Suppl):42-51. PMID: 15223502.

148. Juri H, Palma A, Obeide A. The CO2 laser in the treatment of decubitus ulcer. J Neurol Orth Med Surg. 1986;7(1):29-33.

149. Kierney PC, Engrav LH, Isik FF, et al. Results of 268 pressure sores in 158 patients managed jointly by plastic surgery and rehabilitation medicine. Plast Reconstr Surg. 1998 Sep;102(3):765-72. PMID: 9727442.

150. Yamamoto Y, Tsutsumida A, Murazumi M, et al. Long-term outcome of pressure sores treated with flap coverage. Plast Reconstr Surg. 1997 Oct;100(5):1212-7. PMID: 9326782.

151. Schryvers OI, Stranc MF, Nance PW. Surgical treatment of pressure ulcers: 20-year experience. Arch Phys Med Rehabil. 2000 Dec;81(12):1556-62. PMID: 11128889.

152. Foster RD, Anthony JP, Mathes SJ, et al. Flap selection as a determinant of success in pressure sore coverage. Arch Surg. 1997(a) Aug;132(8):868-73. PMID: 9267271.

153. Foster RD, Anthony JP, Mathes SJ, et al. Ischial pressure sore coverage: A rationale for flap selection. Br J Plast Surg. 1997(b);50(5):374-9. PMID: 9245873.

154. Tavakoli K, Rutkowski S, Cope C, et al. Recurrence rates of ischial sores in para- and tetraplegics treated with hamstring flaps: an 8-year study. Br J Plast Surg. 1999 Sep;52(6):476-9. PMID: 10673925.

155. Foster RD, Anthony JP, Mathes SJ, et al. Ischial pressure sore coverage: a rationale for flap selection. Br J Plast Surg. 1997 Jul;50(5):374-9. PMID: 9245873.

156. Berlowitz DR, Ratliff C, Cuddigan J, et al. The PUSH tool: a survey to determine its perceived usefulness. Adv Skin Wound Care. 2005 Nov-Dec;18(9):480-3. PMID: 16365545.

157. Houghton PE, Campbell KE, Fraser CH, et al. Electrical stimulation therapy increases rate of healing of pressure ulcers in community-dwelling people with spinal cord injury. Arch Phys Med Rehabil. 2010 May;91(5):669-78. PMID: 20434602.

158. Adegoke BO, Badmos KA. Acceleration of pressure ulcer healing in spinal cord injured patients using interrupted direct current. Afr J Med Med Sci. 2001 Sep;30(3):195-7. PMID: 14510128.

159. Adunsky A, Ohry A, Group D. Decubitus direct current treatment (DDCT) of pressure ulcers: results of a randomized double-blinded placebo controlled study. Arch Gerontol Geriatr. 2005 Nov-Dec;41(3):261-9. PMID: 15998547.

160. Ahmad ET. High voltage pulsed galvanic stimulation: effect of treatment durations on healing of chronic pressure ulcers. Indian J Physiother Occup Ther. 2008;2(3):1-5. PMID: 21991123.

161. Baker LL, Rubayi S, Villar F, et al. Effect of electrical stimulation waveform on healing of ulcers in human beings with spinal cord injury. Wound Repair Regen. 1996 Jan-Mar;4(1):21-8. PMID: 17129344.

162. Gentzkow GD, Pollack VP, Kloth LC, et al. Improved healing of pressure ulcers using Dermapulse, a new electrical stimulation device. Wounds. 1991;3(5):158-70.

163. Griffin JW, Tooms RE, Mendius RA, et al. Efficacy of high voltage pulsed current for healing of pressure ulcers in patients with spinal cord injury. Phys Ther. 1991 Jun;71(6):433-42; discussion 42-4. PMID: 2034707.

164. Kloth LC, Feedar JA. Acceleration of wound healing with high voltage, monophasic, pulsed current.[Erratum appears in Phys Ther 1989 Aug;69(8):702]. Phys Ther. 1988 Apr;68(4):503-8. PMID: 3258429.

165. Wood JM, Evans PE, 3rd, Schallreuter KU, et al. A multicenter study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers. Arch Dermatol. 1993 Aug;129(8):999-1009. PMID: 8352625.

166. Gardner SE, Frantz RA, Schmidt FL. Effect of electrical stimulation on chronic wound healing: a meta-analysis. Wound Repair Regen. 1999 Nov-Dec;7(6):495-503. PMID: 10633009.

167. McGaughey H, Dhamija S, Oliver L, et al. Pulsed electromagnetic energy in management of chronic wounds: a systematic review. Phys Ther Rev. 2009;14(2):132-46.

168. Comorosan S, Vasilco R, Arghiropol M, et al. The effect of diapulse therapy on the healing of decubitus ulcer. Rom J Physiol. 1993 Jan-Jun;30(1-2):41-5. PMID: 7982015.

169. Salzberg CA, Cooper-Vastola SA, Perez FJ, et al. The effects of non-thermal pulsed electromagnetic energy (DIAPULSE) on wound healing of pressure ulcers in spinal cord-injured patients: a randomized, double-blind study. Wounds. 1995 1995 Jan-Feb;7(1):11-6.

170. Gupta A, Taly AB, Srivastava A, et al. Efficacy of pulsed electromagnetic field therapy in healing of pressure ulcers: A randomized control trial. Neurol India. 2009 Sep-Oct;57(5):622-6. PMID: 19934563.

171. Aziz Z, Flemming K, Cullum NA, et al. Electromagnetic therapy for treating pressure ulcers. Cochrane Database Syst Rev. 2010;11:CD002930. PMID: 21069672.

172. Speed CAC. Therapeutic ultrasound in soft tissue lesions. Rheumatology (Oxford). 2001;40(12):1331-6.

173. McDiarmid T, Burns PN, Lewith GT, et al. Ultrasound and the treatment of pressure sores. Physiotherapy. 1985;71(2):66-70.

174. Ter Riet G, Kessels AGH, Knipschild P. Randomised clinical trial of ultrasound treatment for pressure ulcers. Br Med J. 1995;310(6986):1040-1. PMID: 7728058.

175. Ter Riet G, Kessels AGH, Knipschild P. A randomized clinical trial of ultrasound in the treatment of pressure ulcers. Phys Ther. 1996;76(12):1301-12. PMID: 8959999.

176. Nussbaum EL, Biemann I, Mustard B. Comparison of ultrasound/ultraviolet-C and laser for treatment of pressure ulcers in patients with spinal cord injury. Phys Ther. 1994 Sep;74(9):812-23; discussion 24-5. PMID: 8066108.

177. Maeshige N, Fujiwara H, Honda H, et al. Evaluation of the combined use of ultrasound irradiation and wound dressing on pressure ulcers. J Wound Care. 2010 Feb;19(2):63-8. PMID: 20216490.

178. Sullivan N, Snyder DL, Tipton K, et al. Negative Pressure Wound Therapy Devices AHRQ Rockville, Maryland: Nov 12 2009. http://www.ahrq.gov/clinic/ta/negpresswtd/negpresswtd.pdf

179. Ford CN, Reinhard ER, Yeh D, et al. Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers. Ann Plast Surg. 2002 Jul;49(1):55-61; discussion PMID: 12142596.

180. Wanner MB, Schwarzl F, Strub B, et al. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. Scand J Plast Reconstr Surg Hand Surg. 2003;37(1):28-33. PMID: 12625392.

181. Ho CH, Powell HL, Collins JF, et al. Poor nutrition is a relative contraindication to negative pressure wound therapy for pressure ulcers: preliminary observations in patients with spinal cord injury. Adv Skin Wound Care. 2010 Nov;23(11):508-16. PMID: 20975334.

182. WHO. UV raditation. World Health Organization; 2012.

183. Wikipedia. Laser. Wikipedia: Wikipedia; 2012.

184. Dehlin O, Elmstahl S, Gottrup F. Monochromatic phototherapy in elderly patients: a new way of treating chronic pressure ulcers?.[Erratum appears in Aging Clin Exp Res. 2003 Dec;15(6):519]. Aging Clin Exp Res. 2003 Jun;15(3):259-63. PMID: 14582689.

185. Dehlin O, Elmstahl S, Gottrup F. Monochromatic phototherapy: effective treatment for grade II chronic pressure ulcers in elderly patients. Aging Clin Exp Res. 2007 Dec;19(6):478-83. PMID: 18172370.

186. Durovic A, Maric D, Brdareski Z, et al. The effects of polarized light therapy in pressure ulcer healing. Vojnosanit Pregl. 2008 Dec;65(12):906-12. PMID: 19160985.

187. Iordanou P, Baltopoulos G, Giannakopoulou M, et al. Effect of polarized light in the healing process of pressure ulcers.[Erratum appears in Int J Nurs Pract 2002 Apr;8(2):116]. Int J Nurs Pract. 2002 Feb;8(1):49-55. PMID: 11831427.

188. Schubert V. Effects of phototherapy on pressure ulcer healing in elderly patients after a falling trauma. A prospective, randomized, controlled study. Photodermatol Photoimmunol Photomed. 2001 Feb;17(1):32-8. PMID: 11169174.

189. Lucas C, Coenen CHM, De Haan RJ. The effect of low level laser therapy (LLLT) on stage III decubitus ulcers (pressure sores); A prospective randomised single blind, multicentre pilot study. Lasers in Medical Science; 2000. p. 94-100.

190. Lucas C, van Gemert MJ, de Haan RJ. Efficacy of low-level laser therapy in the management of stage III decubitus ulcers: a prospective, observer-blinded multicentre randomised clinical trial. Lasers Med Sci. 2003;18(2):72-7. PMID: 12918815.

191. Taly AB, Sivaraman Nair KP, Murali T, et al. Efficacy of multiwavelength light therapy in the treatment of pressure ulcers in subjects with disorders of the spinal cord: A randomized double-blind controlled trial. Arch Phys Med Rehabil. 2004 Oct;85(10):1657-61. PMID: 15468027.

192. Akbari Sari A, Flemming K, Cullum NA, et al. Therapeutic ultrasound for pressure ulcers. Cochrane Database Syst Rev. 2009(1)PMID: 16866964.

193. Arashi M, Sugama J, Sanada H, et al. Vibration therapy accelerates healing of Stage I pressure ulcers in older adult patients. Adv Skin Wound Care. 2010 Jul;23(7):321-7. PMID: 20562541.

194. Burke DT, Ho CHK, Saucier MA, et al. Effects of hydrotherapy on pressure ulcer healing. Am J Phys Med Rehabil. 1998;77(5):394-8. PMID: 9798830.

195. Larking AM, Duport S, Clinton M, et al. Randomized control of extracorporeal shock wave therapy versus placebo for chronic decubitus ulceration. Clin Rehabil. 2010 Mar;24(3):222-9. PMID: 20156981.

196. Edsberg LE, Brogan MS, Jaynes CD, et al. Topical hyperbaric oxygen and electrical stimulation: exploring potential synergy. Ostomy Wound Manage. 2002 Nov;48(11):42-50. PMID: 12426451.

197. Schwien T, Gilbert J, Lang C. Pressure ulcer prevalence and the role of negative pressure wound therapy in home health quality outcomes. Ostomy Wound Manage. 2005 Sep;51(9):47-60. PMID: 16230764.

Abbreviations and Acronyms

Abbreviation/Acronym	Definition
AF	Air fluidized
AHRQ	Agency for Healthcare Research and Quality
ANOVA	Analysis of variance
AP	Alternating pressure
CDC	Center for Disease Control and Prevention
CERs	Comparative Effectiveness Reviews
CHIP	Children's Health Insurance Program
CI	Confidence interval
CLP	Constant low pressure
CO_2	Carbon dioxide
DP	Dextranomer paste
EMT	Electromagnetic therapy
EPC	Evidence-based Practice Center
ET	Electrotherapy
EPUAP	European Pressure Ulcer Advisory Panel
LAL	Low-air-loss beds
NPUAP	National Pressure Ulcer Advisory Panel
NPWT	Negative pressure wound therapy
PICOTs	Populations, Interventions, Comparators, Outcomes, Timing, and Setting
PSST	Pressure Sore Status Tool
PU	Pressure ulcer
PUSH	Pressure Ulcer Scale for Healing
RR	Relative risk
SIP	Scientific information packet
SR	Systematic review
NPWT	Topical negative pressure
TENS	Transcutaneous Electric Nerve Stimulation
TEP	Technical Expert Panel
US	Ultrasound
USPSTF	US Preventative Services Task Force
UVC	Ultraviolet C
WHO	World Health Organization
WSA	Wound surface area